Cover page

Document title: A Phase II Study to Evaluate the Safety, Pharmacokinetics, and Clinical Activity of AZD0171 in Combination with Durvalumab and Chemotherapy in Participants with Locally Advanced or Metastatic Solid Tumours

NCT number: NCT04999969

Date of the Document: 26 September 2024

STATISTICAL ANALYSIS PLAN	
Study Code	D8151C00001
Edition Number	3.0
Date	26-Sep-2024

A Phase II Study to Evaluate the Safety, Pharmacokinetics, and Clinical Activity of AZD0171 in Combination with Durvalumab and Chemotherapy in Participants with Locally Advanced or Metastatic Solid Tumours

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
AUCinf	Area under the concentration-time curve from zero to infinity
AUClast	Area under the concentration-time curve from zero to the last quantifiable concentration
AUCτ	Area under the concentration-time curve in the dose interval
BILI	Total Bilirubin
BOR	Best overall response
BSA	Body surface area
CA19-9	Carbohydrate antigen 19-9
CCr	Creatinine clearance rate
CD8+	Cluster of differentiation 8
CI	Confidence interval
CL	Clearance
Clast	Last observed (quantifiable) concentration
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
COVID-19	Coronavirus Disease 2019
CPS	Clinical Pharmacology Scientist
CR	Complete response
CRF	Case Report Form
CSP/PROTOCOL	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common Terminology Criteria
CV	Coefficient of variation
DBL	Database lock
DCO	Data cut-off

Abbreviation or special term	Explanation
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
gCV	Geometric coefficient of variance
gmean	Geometric mean
GRIm	Gustave Roussy Immune
gSD	Geometric standard deviation
H	High
ICF	Informed Consent Form
IFN-γ	Interferon-gamma
imAE	Immune mediated Adverse Event
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intent-to-treat
L	Low
LD	Longest diameter
LIF	Leukaemia inhibitory factor
LLOQ	Lower limit of quantification
LRV	Lower reference value
LVEF	Left ventricular ejection fraction
MAX	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIN	Minimum
MUGA	Multigated acquisition
N	Normal
NA	Not applicable
NC	Not calculable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not-evaluable
NED	No evidence of disease
NQ	Non-quantifiable

Abbreviation or special term	Explanation
NR	Not reportable
NS	No sample
NTL	Non-target lesion
OAE	Other significant adverse events
OR	Objective response
ORR	Objective response rate
OS	Overall survival
OS-12	Overall survival at 12 months
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
RDI	Relative dose intensity
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SoA	Schedule of Activities
SOC	System organ class
Std Dev	Standard deviation
TEAE	Treatment-emergent adverse events
TFL	Tables, figures, and listings
TL	Target lesion
tlast	Time of last observed (quantifiable) concentration
tmax	Time to maximum observed concentration
TNM	Tumour, nodes, and metastases
TV	Target value
ULN	Upper limit of normal range
WHO	World Health Organisation

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	CCI
N/A	18Jan-2022	Initial approved SAP	N/A	
Data presentation	28-Mar-2023	Additional information provided for the imputation of missing AE and concomitant medication end dates	N/A	
Data presentation	28-Mar-2023	Clarification in the 'Participants Disposition and Completion Status' section about what will be summarised and listed	N/A	
Data presentation	28-Mar-2023	Clarification in the 'Disease Characteristics' section about what will be summarised and at what timepoint	Yes	
Derivation of secondary endpoint(s)	28-Mar-2023	Definition of duration of follow-up for OS added to the 'Secondary Endpoint: Overall Survival' section	Yes	
Derivation of secondary endpoint(s)	28-Mar-2023	Definition of duration of follow-up for PFS censored subjects added to the 'Secondary Endpoint: Progression Free Survival' section	Yes	
Statistical analysis method for secondary endpoint(s)	28-Mar-2023	Clarification in the DoR part of the 'Analyses of Efficacy Endpoints: OS-12, DoR, OS, and PFS' section about the analysis techniques	Yes	
Derivation of secondary endpoint(s)	28-Mar-2023	Updates to the definitions and derivations part and presentation part of the 'Exposure' section	Yes	

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Derivation of secondary endpoint(s)	28-Mar-2023	Updates to the phase and treatment emergent definitions and derivations part of the 'Adverse Events' section	Yes	CCI [redacted]
Data presentation	28-Mar-2023	Clarifications to the presentation part of the 'Adverse Events' section	Yes	
Data presentation	28-Mar-2023	Clarifications to the definitions and derivations part of the 'Clinical Laboratory, Blood Sample' section	N/A	
Data presentation	28-Mar-2023	Clarifications to the presentation part of the 'ADAs against AZD0171 and/or durvalumab in serum' section	Yes	
Statistical analysis method for secondary endpoint(s)	29-Mar-2023	Updates to the 'Pharmacokinetic parameters for AZD0171, durvalumab and chemotherapies and/or their metabolites' section	Yes	
Data presentation	20-Apr-2023	Additional information included regarding approach for multiple ECOG assessments for Baseline recorded on same day without time	Yes	
Data presentation	20-Apr-2023	Additional information included regarding approach for multiple vital signs per participant on same day within time window	Yes	

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Secondary endpoint(s)	20-Apr-2023	Clarification of which study interventions plasma concentrations will be taken for calculation of PK parameters	Yes	CCI [redacted]
Data presentation	20-Apr-2023	Additional information added regarding presentation of imAEs in CSR	Yes	
Data presentation	20-Apr-2023	Updates to presentation of AESI leading to discontinuation specific to each IP	Yes	
Data presentation	20-Apr-2023	Updates to the presentation part of the 'Pharmacokinetic parameters for AZD0171, durvalumab and chemotherapies and/or their metabolites' section	Yes	
Derivation of secondary endpoint(s)	20-Apr-2023	Updates to table of PK parameters & diagnostic parameters to be calculated & presented on study	Yes	
Data presentation	16-Aug-2024	Correction to definition of Interim Response Evaluable Set - change from 17 weeks prior to data extract to 16 weeks. Also listed as a change to protocol planned analyses (Section 2).	No	
Data presentation	16-Aug-2024	Increase in number of patients screened.	Yes	

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Data presentation	16-Aug-2024	Include bullet point for participants discontinued prior to assignment to disposition presentation.	Yes	CCI [redacted]
Derivation of primary endpoint(s)	16-Aug-2024	Removal of participants who have previously withdrawn consent from the scheduled survival sweep.	Yes	
Data presentation	16-Aug-2024	Inclusion of subsequent therapy to on treatment phase definition within the 'Adverse Events' section.	Yes	
Data presentation	16-Aug-2024	Inclusion of immune mediated AE derivations per Durvalumab Charter.	Yes	
Data presentation	16-Aug-2024	Inclusion of definition/derivation for time to onset and time to resolution of AESI/imAE due to complexity of derivation per standards.	Yes	
Data presentation	16-Aug-2024	Removal of Other Significant AEs section	Yes	
Data presentation	16-Aug-2024	Include more details for AESI/imAE outputs.	Yes	

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Primary and secondary analysis methods	16-Sep-2024	Removal of statement regarding possible adjustments for COVID-19 impacts.	Yes	CCI

ADA = Anti-drug antibody; AE = Adverse event; AESI = Adverse event of special interest; AZ = AstraZeneca; CSR = Clinical study report; DoR = Duration of response; ECOG = Eastern Cooperative Oncology Group; imAE = Immune mediated Adverse Event; IP = Investigational Product; OS-12 = Overall survival at 12 months; OS = Overall survival; PFS = Progression-free survival; PK = Pharmacokinetic; SAP = Statistical Analysis Plan; TLF = Tables, figures, and listings;

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis plan for study D8151C00001 supporting the clinical study report (CSR). The reader is referred to v5.0 (dated 03 March 2023) of the clinical study protocol (CSP) and the Case Report Form (CRF) for details of objectives, study design, study conduct, and data collection.

The term "study intervention" throughout the statistical analysis plan (SAP), refers to study treatment/drug (AZD0171, durvalumab, or standard of care chemotherapy). The term "Investigational product" (IP) where used refers to AZD0171 and/or durvalumab.

The study design schema is presented in Figure 1 of the CSP and the Schedule of Activities (SoA) are presented in Appendix D.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

If deemed appropriate, analyses will be performed to explore the impact of Coronavirus Disease 2019 (COVID-19) on the safety, efficacy, and any other endpoints, as appropriate, reported for the study.

Duration required for 2 post-baseline scans within the Interim Response Evaluable Analysis Set has been reduced from 17 weeks to 16 weeks to maximise the number of participants available for analysis by aligning with the minimal frequency per the protocol schedule for 2 post-baseline scans during the Interim Analysis.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

A Safety Review Committee (SRC) will conduct a safety review of the initial approximately 10 to 12 participants after they have completed their first cycle. The SRC may make recommendations regarding continuation, modification, or termination of any study intervention for safety concerns. The safety monitoring of ongoing adverse events (AEs), concomitant medications or therapies, clinical laboratory tests, vital signs, physical examinations, electrocardiograms (ECGs), and echocardiography or multigated acquisition (MUGA) scans (as clinically indicated), including the incidence of dose interruptions, dose modifications, and discontinuations will be reviewed. Safety reviews will be conducted periodically every 6 months. The SRC may request additional data as needed. Additional safety reviews may be conducted at the discretion of the SRC.

An interim analysis of the Objective Response Rate (ORR) will be performed, without pausing enrolment, after approximately 40 dosed participants have had the opportunity to

complete two post-baseline scans. The interim analysis will also include participant disposition and key safety endpoints.

The primary analysis of overall survival at 12 months (OS-12), defined as the proportion of participants alive/surviving at 12 months after initiation of study intervention, will be performed after all dosed participants have had the opportunity for 12 months survival follow-up or died, whichever is sooner.

3.2 Analysis Populations

The following populations are defined:

Table 1 Populations for Analysis

Population/Analysis set	Description	Endpoint/Output
Enrolled	All participants who sign the ICF.	Disposition
Safety	All participants who receive any dose of IP	Exposure Adverse Events Laboratory evaluations Vital Signs/ECG
ITT (primary efficacy analysis)	All participants who receive any dose of study intervention.	Baseline and demography OS OS-12 DCR DoR PFS PFS-4
Response evaluable	All dosed participants who had measurable disease (as per RECIST v1.1) at baseline.	ORR OS-12 (for sensitivity analysis)
Interim response evaluable	All dosed participants who had measurable disease at baseline and who receive first dose at least 16 weeks prior to data extract (where 16 is 2 × the protocolled time between scans.	ORR at interim
PK	All participants who receive at least one dose of study intervention with at least one reportable PK measurement.*	Plasma concentrations and parameters Metabolites PK concentrations and parameters listings
PD	All participants who receive at least one dose of study intervention with at least one reportable PD measurement.	CD8+ T cell Serum CA19-9 Total LIF

Population/Analysis set	Description	Endpoint/Output
Immunogenicity	All participants who receive at least one dose of IP with at least 1 reportable immunogenicity assessment.	ADAs

ADA = anti-drug antibody; CA19-9 = carbohydrate antigen 19-9; CD8+ = cluster of differentiation 8; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ICF = informed consent form; IP = investigational product; ITT = intent-to-treat; LIF = leukaemia inhibitory factor; ORR = objective response rate; OS = overall survival; PD = pharmacodynamics; PFS = progression free survival; PK = pharmacokinetics.
* Individual PK concentration and parameter data for any participants who are excluded from the descriptive summary tables, figures and/or inferential statistical analyses will be included in the listings and flagged with an appropriate footnote.
DoR will be reported for the subset of participants with confirmed objective response.

3.3 General Considerations

3.3.1 General Study Level Definitions

The general principles described below are followed throughout the study:

- Continuous endpoints will be summarised by the number of observations, mean, standard deviation (Std Dev), median, upper and lower quartiles (as applicable), minimum, and maximum. For data that requires log-transformation, geometric mean, coefficient of variation (CV), median, minimum, and maximum will be presented. Categorical endpoints will be summarised by frequency counts and percentages for each category.

- Unless otherwise stated, percentages will be calculated out of the analysis set total (excluding efficacy and exposure).

- For continuous data, descriptive summary statistics (mean, median, standard deviation, standard error, confidence intervals [CIs]) will be rounded to one additional decimal place compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.

- Derived variables will be rounded to one more decimal place compared to the least number of decimal places among the raw data used for calculation, provided the scale of the data is not changing.

- For categorical data, percentages will be rounded to one decimal place.

- SAS® version 9.4 *(as a minimum)* will be used for all analyses.

- Baseline is the last non-missing value obtained immediately prior to the first dose/administration of any study intervention and any information taken after first dose/administration of study intervention is regarded as post-baseline information. In the scenario where there are two assessments on Day 1 prior to first dose, one with time recorded and the other without time recorded, the one with time recorded

will be selected as baseline. If multiples visits are equally eligible to assess participants status at baseline (eg, screening and baseline assessments are both on the same date prior to first dose/administration with no washout or other intervention in the screening period), the average will be taken as the baseline value. For non-numeric laboratory tests (ie, some of the urinalysis parameters) where taking an average is not possible then the value closest to the normal will be taken as baseline as this is the most conservative. For multiple Eastern Cooperative Oncology Group (ECOG) assessments on the same day where time of assessment was not recorded then the 'worst' case scenario (ie, highest ECOG score) to capture any possible PD.

- Where safety data are summarised over time, study day is calculated in relation to date of first treatment. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, serves as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured is considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

- In all summaries, change from baseline endpoints will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value - baseline value) / baseline value × 100. For any endpoint subjected to log transformation, the change from baseline calculated and summarised on the log scale will be back-transformed and presented as a 'baseline scaled ratio' (BSR). Percentage change will then be calculated as (BSR - 1) × 100.

- Exact CIs for proportions will be calculated using the exact binomial distribution (Clopper-Pearson method).

- Unless stated otherwise, two-sided 80% CI will be produced for clinical estimates and 90% CI for pharmacokinetics (PK)/pharmacodynamics (PD) estimates.

- For percentiles of survival times based on the Kaplan-Meier method (eg, median survival), CI will be calculated using the default method available in the SAS LIFETEST procedure (ie, the Klein and Moeschberger extension of the Brookmeyer-Crowley method).

- For point-estimates of survival based on the Kaplan-Meier method (eg, for progression-free survival [PFS]), CI will be calculated using the default method available in the SAS LIFETEST procedure (ie, using Greenwood's estimate of standard error and a log-log transformation).

- Missing safety data will generally not be imputed. However, safety assessment values of the form of "<x" (ie, below the lower limit of quantification) or >x

(ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings. See Section 4.10.1 for handling of PK parameters in terms of lower limit of quantification.

3.3.2 Visit Window

For safety, time windows are defined for any presentations that summarise values by visit. The following conventions apply:

- The time windows are exhaustive so that data recorded at any timepoint has the potential to be summarised. Inclusion within the time window is based on the actual date and not the intended date of the visit.
- All unscheduled visit data have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half-way between the two visits (the lower limit of the first post-baseline visit is Day 2). If an even number of days exists between two consecutive visits, then the upper limit is taken as the midpoint value minus 1 day. The visits for Screening and Cycle 1 Day 1 will be excluded from remapping. The window for the end of treatment visit will be between the date of the last dose up to the date of the last dose plus 14 days. Follow-up visit will be mapped to the follow-up schedule as shown in Table 3 Overall visit responses.

For example, the visit windows for vital signs data are:

Table 2: Visit Windows

Cycle	Day	Planned Day	Visit Window
1	1	Day of first dose in cycle 1	exact
1	8	8	2–11
1	15	15	12–21
2	1	29	22–32
2	8	36	33–39
2	15	43	40–49
3	1	57	50–60
3	8	64	61–67
3	15	71	68–77
4	1	85	78–88
4	8	92	89–95
4	15	99	96–105

Table 2: Visit Windows			
5	1	113	106–116
5	8	120	117–123
5	15	127	124–133
6	1	141	134–144
6	8	148	145–151
6	15	155	152–161
7	1	169	…

Windows for follow-up visits are:

Table 3: Follow-up visit windows		
Follow-up Visit	**Planned Day**	**Visit Window**
End of Treatment	Last dose	0 - 14
FUP-1	28 post last dose	15 – 58
FUP-2	90 post last dose	59 – 114

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings display all values contributing to a time point for a participant.
- For visit-based summaries, if there is more than one value per participant within a time window then the closest value to the scheduled visit date will be summarised, or the earlier, in the event the values are equidistant from the nominal visit date. For instances of multiple values per participant recorded on the same day within time window then the latest value prior to dosing will be summarised. The listings should highlight the value for the participant that contributed to the summary table, wherever feasible. The visit will be missing if no assessment was reported within the specified visit window around the planned study day. Note: in summaries of extreme values, all post baseline values collected will be used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
- For summaries at a participant level, all values will be included, regardless of whether they appear in a corresponding visit-based summary, when deriving a participant level statistic such as a maximum.

3.3.3 Handling of Unscheduled Visits

See Section 3.3.2 for safety.

3.3.4 Handling of Protocol Deviations in the Study Analysis

According to ICH E3 guidelines version dated 1995 (ICH 1995),

"Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety or well-being."

Important Protocol Deviations (IPDs) may include, but are not limited to the following:

- Written informed consent not obtained prior to mandatory study specific procedures, sampling and analyses
- Participants who did not meet inclusion criteria or met exclusion criteria, and received study intervention
- Participants assigned to study intervention who received their study intervention at > 10% deviation to that assigned on one or more occasions
- Participants who received prohibited concomitant medications during study period
- Participants who met study intervention discontinuation criteria but continued study intervention, and potentially had major impact to safety of participants according to clinical judgement
- Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) scans performed outside of the scheduled window on more than two occasions
- Missing RECIST v1.1 assessments for efficacy for two consecutive assessments

None of the deviations lead to participants being excluded from any analysis populations described in the SAP, unless otherwise specified. If a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed. A list of all protocol deviations will be reviewed and decisions regarding how to handle these deviations will be documented in the electronic Trial Master File (eTMF) by the study team physician, clinical pharmacology scientist and statistician prior to database lock (DBL).

3.3.5 Missing Dates

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events or concomitant medications (including palliative radiotherapies). Flags are retained in the database indicating where any programmatic imputation has been applied. The imputed dates should not be used to calculate durations, where the results would be less accurate.

The following rules will be applied when partial dates are detected in the study:

- For missing diagnostic dates (eg, disease diagnosis), if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.
- For missing AE and concomitant medication start dates, the following will be applied:
    a. Missing day - impute the 1st of the month unless month is the same as month of the first dose of study drug then impute first dose date.
    b. Missing day and month - impute 1st January unless year is the same as first dose date then impute first dose date.
    c. Completely missing - impute as first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.
    d. Imputed start date should be no later than the end date. If imputed start date is later than the end date, then set to end date.
- For missing AE and concomitant medication end dates, the following is applied:
    a. Missing day - impute the last day of the month unless both the month and the year are the same as the last dose date or the primary analysis data cut-off (DCO) date then impute the last dose date or the primary analysis DCO date, respectively.
    b. Missing day and month - impute 31st December unless the year is the same as the last dose date or the primary analysis DCO date then impute the last dose date or the primary analysis DCO date.
    c. Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date and when it started in relation to study drug. If the ongoing flag is missing, then assume that AE is still present / medication is still being taken (ie, do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute first dose date or if it started on or after first dose date then impute a date that is on or after the last dose of study drug date or the primary analysis DCO date.

- If a participant is known to have died, as recorded in CRF pages AE, serious adverse event (SAE) Report, Disposition, Discontinuation of IP (AZD0171), Discontinuation of IP (durvalumab), Death Details and ECOG Performance Status, where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive + 1 from the database and the imputed death date using the available information provided:

  a. For Missing day only – using the 1st of the month.

  b. For Missing day and Month – using the 1st of January.

3.3.6 Sample Size

Approximately 370 participants will be screened/enrolled to achieve up to 115 evaluable participants.

"Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

CCI [redacted]

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation, and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participants disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication, and study drug compliance.

4.1.1 Participants Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Study participation (ie, a participant is "enrolled") is defined in protocol Section 9.2.
Completion of treatment is defined in protocol Section 4.4.

4.1.1.2 Presentation

Participant disposition including screen failures and reason for screen failure will be summarised and listed based on all participants screened (ie, informed consent received). The number and percentage of participants for the following will be summarised, where percentages related to screening and discontinuation prior to assignment will based upon participants screened and all others will be based upon participants assigned to treatment:

- Participants screened;
- Participants who screen failed;
- Reason for screen failures;
- Participants discontinued prior to assignment
- Participants assigned to treatment;
- Participants assigned to treatment, but who were not treated;
- Participants who started treatment;
- Participants who discontinued treatment, ie, discontinued any part of the study intervention (presented separately for each study intervention);
- Reasons for treatment discontinuation – presented separately for each study intervention;
- Participants ongoing study treatment at DCO date;
- Participants ongoing study at DCO date;
- Participants who withdrew from study (including due to global/country situation);
- Reasons for withdrawal from the study.

The number of participants who continue receiving IP after the first overall time point assessment of progressive disease by RECIST v1.1 will be summarised.

The number of participants by region, country, and centres and disruptions due to global/country situation will also be summarised. The number of participants with confirmed/suspected COVID-19, and number of participants with confirmed/suspected COVID-19 who died will also be presented for the Intention-to-Treat (ITT) analysis set.

Listings will be presented for:

- Disposition details for discontinued participants and participants ongoing in the study.
- Participants affected by the global/country situation, along with a listing specifying the details of the reported issue due to the global/country situation.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

For the definitions of each analysis set, refer to Section 3.2.

4.1.2.2 Presentation

The number of participants in each analysis set will be presented for all participants. Any exclusions from analysis sets will be listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important Protocol Deviations are those that could have a large influence on the interpretation of any analysis based on addressing the primary and secondary objectives of the trial. The list of the categories is presented in Section 3.3.4.

Programmable protocol deviations will be detected from the data recorded in the clinical database and will be reviewed at regular protocol deviation review meetings. At this meeting, the programmatically derived protocol deviations will be checked to ensure that they have been correctly classified as important or other study deviations.

On an ongoing basis throughout the study, monitoring notes or summaries will also be reviewed to determine any important post-entry deviations that are not identifiable via programming.

If the number of deviations which are considered to have the potential to impact the primary analysis is considered important, sensitivity analyses may be performed on subgroups. This will be decided during the data review meeting and before DBL.

4.1.3.2 Presentation

The incidence of IPDs will be summarised by deviation categories for the ITT analysis set. The number and percentage of participants in the following categories will be summarised:

- Number of participants with at least one IPD;
- Number of participants with at least one global/country situation related IPD;
- Number of participants with at least one IPD, excluding global/country related IPDs.

A listing will be provided with the IPD details.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Age (years) will be grouped accordingly: < 50, ≥ 50 - < 65, ≥ 65 - < 75, and ≥ 75. Each race category counts participants who selected only that category.

4.1.4.2 Presentation

Demographics will be summarised and listed based on the ITT analysis set (unless otherwise specified). Standard descriptive statistics will be presented for the continuous variables. Counts and percentages of participants will be presented for the categorical variables. The following will be summarised:

- age (years)
- age group
- sex
- race
- ethnicity

Demographic characteristics in participants with confirmed/suspected COVID-19 infection will also be summarised and listed similarly.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Body mass index (BMI) (kg/m^2) will be calculated as: weight/(height^2). Body Surface Area (BSA) (m^2) will be derived using the Du Bois formula: 0.007184 x $weight^{0.425}$ x $height^{0.725}$.

Weight (kg) will be grouped accordingly: < 50, ≥ 50 - < 70, ≥ 70 - ≤ 90 and > 90, and BMI will be grouped accordingly: < 18.5, ≥ 18.5 - < 25.0, ≥ 25.0 - < 30.0 and ≥ 30.0.

4.1.5.2 Presentation

Baseline characteristics will be summarised and listed for the ITT analysis set. The following will be summarised:

- height (cm)
- weight (kg)
- weight group
- BMI (kg/m^2)
- BMI group
- BSA (m^2)

Standard descriptive statistics will be presented for the continuous variables. Counts and percentages of participants will be presented for the categorical variables.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Time from original diagnosis to first dose will be calculated as: (Date of first dose – date of original diagnosis) +1 / (365.25/12).

Time from metastatic disease to first dose will be calculated as: (Date of first dose – date of metastatic disease) +1 / (365.25/12).

4.1.6.2 Presentation

Disease characteristics at baseline will be listed and summarised for the ITT analysis set.

Summaries will be produced that present the number and percentage of participants on their:

- Eastern Cooperative Oncology Group (ECOG) performance status at baseline
- Gustave Roussy Immune Score (GRIm-Score) at baseline
- Primary tumour location at diagnosis
- Histology type at diagnosis
- Tumour grade at time of diagnosis

- American Joint Committee on Cancer (AJCC) stage at diagnosis
- Tumour, node, and metastases (TNM) classification for primary tumour at time of diagnosis
- Metastatic sites at baseline
- Sites of local/metastatic disease at baseline.

Summary statistics will also be presented for participants' time from original diagnosis to first dose, time from metastatic disease to first dose, CA19-9 at baseline, number of target and non-target lesions, and sum of target lesions (longest diameter [or short axis for lymph nodes], mm).

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history and relevant surgical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

4.1.7.2 Presentation

Medical history and concomitant disease will be listed and summarised for the ITT analysis set by system organ class (SOC) and preferred term (PT). Medical history for participants with confirmed/suspected COVID-19 infection will be summarised and listed similarly.

All relevant surgical history will be listed and summarised similarly.

Previous Disease-Related Treatment Modalities

Summaries of the number and percentage of participants who have had previous disease-related treatments permitted in Section 5.2 of the CSP, will be presented for each type of modality (systemic therapy, radiation, cancer related surgery, others).

Prior Anti-cancer Treatment

The number and percentage of participants who have had prior anti-cancer treatments permitted in Section 5.2 of the CSP will be summarised. The agents received and best response in most recent regimen will be listed.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

All prior and concomitant medications will be captured in the electronic Case Report Form (eCRF).

Other anti-cancer therapies, investigational agents, and non-palliative radiotherapy should not be given while the participant is on study drug.

For the purpose of inclusion in prior and/or concomitant mediation or therapy summaries, incomplete medication or radiotherapy start and stop dates will be imputed as detailed in Section 3.3.5.

Prior medications, concomitant and post-treatment medications are defined based on imputed start and stop dates (and potentially flags from the eCRF) as follows:

- Prior medications are those taken prior to study intervention with a stop date prior to the first dose of study intervention. If medication is flagged as prior and the prior medication stop date is partial (only month and year available), and the month and year is the same as the study intervention start date, then medication will be assigned as prior.
- Concomitant medications are those with a stop date on or after the first dose date of study intervention and must have started prior to or during treatment so there is at least one day in common with the study intervention or started up to 90 days after the last dose date of study intervention.
- Post-treatment medications are those with a start date beyond 90 days after the last dose date of study intervention.

4.1.8.2 Presentation

The number and percentage of participants who took prior and concomitant medications will be summarised and listed by Anatomical therapeutic chemical (ATC) decode and the generic name/term coded by World Health Organisation (WHO) Drug Dictionary.

4.1.9 Post Anti-Cancer Treatment

The number and percentage of participants who have had post anti-cancer treatments and agents received will be summarised.

4.2 Efficacy Endpoints

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Table 4: Efficacy Endpoints
Objective 1: To determine the preliminary OS of AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC

Table 4: Efficacy Endpoints					
Primary	Overall Survival at 12 months	ITT	Participants included in analysis regardless of treatment discontinuation, study withdrawal or participant receives subsequent cancer therapy.	Proportion of participants alive/surviving at 12 months after initiation of study intervention and associated two-sided 80% CI using the Kaplan-Meier method	
Primary	Overall Survival at 12 months (sensitivity analysis)	Response evaluable	Participants included in analysis regardless of treatment discontinuation, study withdrawal or participant receives subsequent cancer therapy.	Proportion of participants alive/surviving at 12 months after initiation of study intervention and associated two-sided 80% CI using the Kaplan-Meier method	REF _Ref86059803 \r \h 4.7.2
Objective 2: To further characterise the preliminary (i) antitumour activity and (ii) survival activity of AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC					
Secondary	Objective Response Rate	Response evaluable	Response must be before subsequent cancer therapy and before progression.	Rate and 80% CI	REF _Ref178086507 \r \h 4.7.3
Secondary	Disease Control Rate	ITT	Response or stable disease (SD) must be before subsequent cancer therapy.	Rate and 80% CI	REF _Ref178086507 \r \h 4.7.3
Secondary	Duration of Response	ITT	Response must be before subsequent cancer therapy and before progression.	Median event time with 2-sided 80% CI	REF _Ref178086536 \r \h 4.7.1

Table 4: Efficacy Endpoints					
Secondary	Overall Survival	ITT	Participants included in analysis regardless of treatment discontinuation, study withdrawal or participant receives subsequent cancer therapy.	Median event time with 2-sided 80% CI	4.7.1
Secondary	Progression Free Survival	ITT	Participants are followed until first progression or death even if on subsequent cancer therapy (treatment policy). If participants progress or die after 2 or more consecutive missed visits they are censored prior to the 2 missed visits.	Median and 80% CI	REF _Ref178086596 \r \h 4.7.1

CI = Confidence Interval; ITT = Intention-to-Treat; mPDAC = metastatic pancreatic ductal adenocarcinoma

Efficacy analyses, except for overall survival (OS), are based on programmatic application of RECIST v1.1 (Eisenhauer et al, 2009) to investigator assessed tumour measurements. Programmatic derivation guidance used for the application of RECIST v1.1 are provided in Appendix A, which is used to determine disease response.

RECIST v1.1 data, overall visit response and best overall response (BOR) will be listed.

All efficacy analyses, with the exception of ORR, will be presented for the ITT analysis set.

4.2.1 Primary Endpoint: Overall Survival at 12 months

The primary efficacy endpoint is OS-12.

Overall survival is defined as the time from the date of first dose until death due to any cause regardless of whether the participant withdraws from study therapy or receives another anti-cancer therapy. Overall Survival at 12 months (OS-12) is defined as the proportion of participants alive/surviving at 12 months after initiation of study intervention. The Kaplan-Meier method will be used to estimate the OS curve on the ITT analysis set. Participants will be censored on the last date when participants are known to be alive.

Refer to Section 4.2.5.1 for the derivation of OS-12.

4.2.2 Secondary Endpoint: Objective Response Rate

Objective Response Rate is a secondary endpoint.

The ORR is based on the site investigator RECIST v1.1 data and using all scans regardless of whether they were scheduled or not.

Objective Response (OR) is defined as a confirmed best overall response of CR or PR that occurs prior to the initiation of subsequent anticancer treatment and prior to progression. Objective Response Rate is defined as the percentage of participants with objective response, with the denominator defined as the number of participants in the response evaluable set.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 28 days (4 weeks) after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, are included in the assessment of ORR. Also, only data obtained before the start of subsequent anticancer treatment (excluding radiotherapy) are included. Therefore, both visits contributing to a confirmed response must be prior to progression and prior to subsequent anticancer treatment.

In the case where a participant has two non-consecutive visit responses of PR, then, as long as the time between the two visits of PR is greater than 4 weeks and there is no PD between the PR visits, the participants is defined as a responder. Similarly, if a participant has visit responses of CR, Not-evaluable (NE), CR, then, as long as the time between the two visits of CR is greater than 4 weeks, then a best response of CR is assigned.

4.2.3 Secondary Endpoint: Disease Control Rate

Disease Control Rate (DCR) is a secondary endpoint.

Disease control is defined as the percentage of participants with a BOR of confirmed CR or PR or having SD (without subsequent cancer therapy) maintained for ≥ 16 weeks from first

dose, where 16 weeks is the DCR time point. Disease control rate at 16 weeks (DCR-16) is defined as the percentage of participants who have disease control.

4.2.4 Secondary Endpoint: Duration of Response

Duration of Response (DoR) is a secondary endpoint.

Duration of Response (DoR) is defined as the time from the date of first documented objective response (confirmed CR or confirmed PR) until date of first documented disease progression or death (by any cause in the absence of disease progression). Duration of response will be measured for responding participants (participants with confirmed CR or confirmed PR) only.

4.2.4.1 Derivations

DoR (months) = (date of PFS event (progression/death) or censoring – date of first objective response that is subsequently confirmed + 1) / (365.25/12)

The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response is defined as the latest of the dates contributing towards the first visit response of CR or PR (which was subsequently confirmed). If a participant does not progress following a response, then their DoR will be censored on the PFS censoring date. Only participants who have achieved objective response (confirmed CR or confirmed PR) will be evaluated for DoR.

4.2.5 Secondary Endpoint: Overall Survival

Overall Survival is a secondary endpoint.

Overall survival is defined as the time from the date of first dose until death due to any cause regardless of whether the participant withdraws from study therapy or receives another anti-cancer therapy. If there is no death reported for a participant before the DCO for the OS analysis, OS will be censored at the last contact date at which the participant is known to be alive.

4.2.5.1 Derivations

OS (months) = (date of death or censoring (date last known to be alive) – date of first dose + 1) / (365.25/12)

Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive from the Survival Status CRF page only.

Survival calls will be made in the week following the date of DCO for the analysis, and if participants are confirmed to be alive or if the death date is post the DCO date these

participants will be censored at the date of DCO. The status of ongoing and "lost to follow-up" participants at the time of the final OS analysis should be obtained by the site personnel by checking the participant's notes, hospital records, contacting the participant's general practitioner, and checking publicly-available death registries. In the event that the participant has actively withdrawn consent to the study or the processing of their personal data, the vital status of the participants will not be collected and participants will be censored at date last know alive as defined as the latest among dates defined in Section 4.7.1.

For any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the participant was known to be alive for those participants still on treatment (since the SURVIVE module is only completed for participants off treatment if a survival sweep is not performed). The last date for each individual participant is defined as the latest among dates defined in Section 4.7.1.

Duration of follow-up for OS is reported separately for censored subjects and non-censored subjects and is defined as follows: Duration of follow-up for OS (months) = (date of death or censoring (date last known to be alive) – date of first dose + 1) / (365.25/12).

4.2.6 Secondary Endpoint: Progression Free Survival

Progression Free Survival is a secondary endpoint.

Progression Free Survival is defined as the time from first dose until date of first documented disease progression or death (by any cause in the absence of disease progression), regardless of whether the participant withdraws from study therapy or receives another anti-cancer therapy prior to progression.

4.2.6.1 Derivations

PFS (months) = (date of PFS event (progression/death) or censoring – date of first dose + 1) / (365.25/12)

Participants who have not progressed or died at the time of analysis are censored at the time of the latest date of assessment from their last evaluable disease assessment. However, if the participant progresses or dies after two or more consecutive missed visits, the participant will be censored at the time of the latest evaluable disease assessment prior to the two missed visits. Note: a NE visit is not considered as a missed visit.

Given the scheduled visit assessment scheme (ie, 8-weekly for the first 48 weeks then 12-weekly thereafter) the definition of two missed visits changes.

If the previous RECIST v1.1 assessment is less than study Day 50 (ie, Week 7) then two missing visits equates to 17 weeks since the previous RECIST v1.1 assessment, allowing for a late visit (ie, 2 x 8 weeks + 1 week for a late assessment = 17 weeks).

If the previous RECIST v1.1 assessment is greater than or equal to study day 50 and less than study Day 274 (ie, Week 39) then two missing visits equates to 18 weeks since the previous RECIST v1.1 assessment, allowing for early and late visits (ie, 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks).

If the two missed visits occur over the period when the scheduled frequency of RECIST v1.1 assessments changes from 8-weekly to 12-weekly this equates to 22 weeks (ie, take the average of 8 and 12 weeks which gives 10 weeks and then apply same rationale, hence 2 x 10 weeks + 1 week for an early assessment + 1 week for a late assessment = 22 weeks). The time period for the previous RECIST v1.1 assessment is from study Days 274 to 329 (ie, Week 39 to Week 47).

From week 47 onwards (when the scheduling changes to 12-weekly assessments), two missing visits equates to 26 weeks (ie, 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks).

If the participant has no evaluable disease assessments post-baseline or does not have baseline tumour assessment data, they are censored at Day 1 unless they die within two visits of baseline (16 weeks plus 1 week allowing for a late assessment within the visit window) when the death qualifies as a PFS event. Participants who are censored at Day 1 are included in the ITT analysis set and the analysis but they do not contribute to any risk set or PFS. For participants who met one or more censoring conditions, PFS will be censored according to the earliest censoring condition; for participants who met none of the censoring conditions, PFS will be calculated by the earliest PFS event date.

A summary of censoring rules and the date of PD/death or censoring are given in Table 5. Note that censoring overrides event in certain specified cases.

Table 5 Summary of Censoring Rules for PFS

Situation	Date of PD/Death or Censoring	PFS Outcome
Documented PD or death in the absence of progression	Date of earliest documentation of PD or date of death in the absence of progression	Event
Either no tumour assessment at baseline or no evaluable assessments post-baseline AND death prior to second scheduled post-baseline disease assessment	Date of death	Event

Table 5 Summary of Censoring Rules for PFS

Situation	Date of PD/Death or Censoring	PFS Outcome
Either no tumour assessment at baseline or no evaluable assessments post-baseline AND no death prior to second scheduled post-baseline disease assessment	Date of first dose (Day 1)	Censored
PD or death (in the absence of progression) immediately after ≥ 2 consecutive missed disease assessments as per the protocol specified assessment schedule	Last evaluable progression-free disease assessment prior to missed assessments	Censored
At least one post-baseline tumour assessment, on-going with neither PD nor death at the time of analysis or lost to follow-up or withdrawn consent	Date of last evaluable disease assessment	Censored
Initiation of subsequent anti-cancer treatment prior to PD or death	Date of last evaluable disease assessment prior to initiation of subsequent anticancer treatment	Censored for Sensitivity Analyses only

PD = progressive disease; PFS = progression-free survival

The PFS time is always derived based on scan/assessment dates, not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules are applied:

- The date of progression is determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a participant for PFS the participant is censored at the latest of the dates contributing to a particular overall visit assessment.

Note: for target lesions (TLs) only the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for non-target lesions (NTLs) only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

The proportion of participants alive and progression free at 4 months (PFS-4) is defined as the Kaplan-Meier estimate of PFS (per RECIST v1.1 as assessed by the site investigator) at 4 months.

Duration of follow-up for PFS is applicable only for PFS censored participants and is defined as follows: Duration of follow-up for PFS in censored subjects (months) = (date of PFS censoring – date of first dose + 1) / (365.25/12).

4.3 Safety Endpoints

4.3.1 Primary Endpoints: AEs, Immune Mediated AEs and Serious AEs, Laboratory Evaluations, Vital Signs, and ECG Results

Analysis methods for the primary safety endpoints are described in Section 4.8.

4.3.2 Secondary Endpoint: ADAs against AZD0171 and/or Durvalumab in Serum

Analysis methods for the secondary safety endpoint are described in Section 4.8.8.

4.4 Pharmacodynamic Endpoints

4.4.1 Secondary Endpoint: Assessment of CD8+ T Cell Tumour Infiltration in Tumour Samples at Baseline and on-Treatment

Tissue obtained as part of the screening procedure and mandatory/optional biopsies obtained during treatment will be assessed for CD8+ T cell tumour infiltration.

4.4.2 Secondary Endpoint: Serum CA19-9

Serum levels of CA19-9 will be used to evaluate preliminary antitumour activity of AZD0171 in combination with durvalumab and chemotherapy.

4.4.3 Secondary Endpoint: Total Leukaemia Inhibitory Factor

Total leukaemia inhibitory factor (LIF) will be collected for measurement of study intervention concentrations.

4.4.4 CCI

CCI

CCI

4.5 Pharmacokinetic Endpoints

4.5.1 Secondary Endpoint: Pharmacokinetic Parameters for AZD0171, Durvalumab and Chemotherapies and/or their Metabolites

Summary of concentrations and PK parameters for AZD0171, durvalumab and chemotherapies and/or their metabolites is a secondary PK endpoint.

Serum samples (AZD0171 and durvalumab) and plasma samples (gemcitabine and nab-paclitaxel) will be collected for measurement of study intervention concentrations as specified in the SoA. The PK parameters of the concentration data for AZD0171, Durvalumab, chemotherapies and/or their metabolites (if metabolite(s) are defined and their concentrations are available) are derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara) by AztraZeneca.

Intensive PK sampling will be collected from the 10 to 12 safety run-in participants. Non-intensive PK sampling will be collected in the first 40 participants only (including the run-in participants, ie, 10 to 12 safety run-in participants plus 28 to 30 non-intensive participants).

Individual sampling timepoints are provided in the CSP Table 18, Table 19, and Table 20 for AZD0171 and total LIF, in the CSP Table 21 and Table 22 for durvalumab, and in the CSP Table 23 and Table 24 for chemotherapy.

All participants who receive any amount of study intervention with at least one reportable PK measurement will be evaluated.

Details of population PK, PK/pharmacodynamic relationships, and/or exposure response/safety analyses will be described separately from this SAP. The population PK analysis will be presented separately from the main CSR.

4.5.2 CCI [redacted]

CCI [redacted]

4.6 CCI [redacted]

CCI [redacted]

4.7 Analyses of Efficacy Endpoints

4.7.1 Overall Survival at 12 months, Duration of Response, Overall Survival and Progression Free Survival

The OS curve will be censored on the last date when participants are known to be alive. If the Survival Status CRF is not completed for certain participants, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the participant was

known to be alive for those participants still on treatment. The last date of each individual participant is defined as the latest among the following dates recorded on the eCRF:

- AE start, stop and change in severity dates
- Admission and discharge dates of hospitalization
- Study intervention (infusion) dates
- End of treatment dates
- Concomitant medication start and stop dates
- Laboratory test dates
- Dates of vital signs
- Disease assessment dates on RECIST v1.1 CRF
- Start and stop dates of alternative anti-cancer therapy
- Dates last know alive on survival status CRF
- End of study date

If a participant is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- For Missing day only – using the 1st of the month.
- For Missing day and Month – using the 1st of January.

If there is evidence of death but the date is entirely missing, it is treated as missing, (ie, censored at the last known alive date).

Overall Survival at 12 months

The analysis of OS-12 will be based on the ITT analysis set. The proportion of participants alive at 12 months (OS-12) and associated two-sided 80% CI will be estimated using the Kaplan-Meier method. Kaplan-Meier plots of the OS will also be presented. The primary analysis will be performed after all dosed participants have had the opportunity for 12 months survival follow-up or died, whichever is sooner.

Duration of Response

The analysis for DoR will be based on the ITT analysis set. DoR will be summarised and graphically presented using the Kaplan-Meier method. The median DoR and 2-sided 80% CI are estimated using the Kaplan-Meier method. In addition, the event-free probability at different time points, eg, 3, 6, 9 months, etc., will be estimated with corresponding 2-sided 80% CIs using the Kaplan-Meier technique. These time points may be adjusted according to actual data observed in the study without amendment to this SAP. Swimmer plots that show the profile of each participant who responds will be produced.

Overall Survival

The analysis of OS will be based on the ITT analysis set. OS will be summarised using the same methodology described in the DoR section, with the exception that summaries of the number and percentage of participants who have died, those still in survival follow-up, those lost to follow-up and those who have withdrawn consent will be provided.

A summary of the duration of follow-up for OS is included using median (range). This is presented separately for censored and non-censored participants.

Progression Free Survival

The analysis of PFS will be based on the ITT analysis set. The number and percentage of participants experiencing a PFS event broken down by type of event/censoring and Kaplan-Meier plots of PFS will be presented. The median PFS and its two-sided 80% CI will be estimated using the Kaplan-Meier method, if participant numbers allow.

The treatment status at progression of participants at the time of analysis will be summarised. This includes the number and percentage of participants who were on treatment at the time of progression, the number and percentage of participants who discontinued study intervention prior to progression, the number percentage of participants who have not progressed and were on treatment or discontinued treatment.

A summary of the duration of follow-up for PFS will be included using median (range). This will be presented only for censored participants (including all types of PFS censoring).

The proportion of participants alive and progression free at 4 months and associated 2-sided 80% CI will be estimated using the Kaplan-Meier method

4.7.2 Sensitivity Analysis of OS-12

A sensitivity analysis of OS-12 will be performed based on the response evaluable set.

4.7.3 Objective Response Rate and Disease Control Rate

Objective Response Rate

ORR is based on the response evaluable set. Summaries will be produced to present the number and percentage of participants with a confirmed overall response of CR or PR. The ORR will be presented with a 2-sided 80% CI using the Clopper-Pearson (exact probability) method. The main analysis of ORR is based on the Response evaluable set. For the computation of ORR, participants with BOR of 'NE' will be included in the response evaluable set and will be considered non-responders.

Disease Control Rate

The main analysis of DCR will be based on the ITT analysis set. The number and percentage of participants with a DCR will be presented, with a 2-sided 80% CI using the Clopper-Pearson (exact probability) method.

4.7.4 Sensitivity Analyses for Irradiated Lesions/Lesion Intervention

Sensitivity analyses will be performed if there are participants who have any TL intervention during the study that was not specified within the protocol. The analyses that may require a sensitivity analysis are: DoR, PFS, ORR, and DCR.

The scaling for sensitivity analysis is described in Appendix A.

4.8 Analyses of Safety Endpoints

The domain safety covers exposure, AEs, clinical laboratory, vital signs, and ECGs.

Tables will be provided for the safety set, listings will be provided for all participants or the safety set depending on the availability of data.

4.8.1 Exposure

4.8.1.1 Definitions and Derivations

- Duration of exposure (months) will be defined separately for each study intervention as follows:
  - Duration of exposure (months) of AZD0171 = (last date of actual dosing (ie, a dose > 0 [mg] was given) in the last cycle + 13 days (the number of days until the next scheduled dose minus one day) – first dose date + 1) / (365.25/12)
  - Duration of exposure (months) of durvalumab = (last date of actual dosing (ie, a dose > 0 [mg] was given) in the last cycle + 27 days (the number of days

until the next scheduled dose minus one day) – first dose date + 1) / (365.25/12).

- Duration of exposure (months) of chemotherapy (gemcitabine and nab-paclitaxel) = (last date of actual dosing (ie, a dose > 0 [mg] was given) in the last cycle + 6 days (the number of days until the next scheduled dose minus 1 day) if last date of dosing is Day 1 or Day 8 of a cycle, or +13 days (the number of days until the next scheduled dose minus 1 day) if last date of dosing is Day 15 of a cycle – first dose date + 1) / (365.25/12).

- For participants who die whilst on study intervention or if a DCO occurs, duration of exposure (months) is defined as (the minimum of (DCO date, last dose + cycle length or days until the next scheduled dose minus one day, death date) – the first dose date + 1 day) / (365.25/12).

- Duration of exposure (cycles) is defined as the number of cycles in which at least one portion of study treatment was administered (ie, dose > 0 mg). If a cycle is prolonged due to toxicity, this should still be counted as one cycle.

- Actual duration of exposure (months) = duration of exposure – total duration of dose interruptions, where duration of exposure is calculated as described above. Dose interruptions are any periods when the participant does not take any treatment. For handling participants who permanently discontinue during a dose interruption, refer to Appendix B.

- Dose intensity of study interventions is addressed by considering relative dose intensity (RDI), where RDI is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. More specifically, RDI is defined as follows:

    - RDI = 100% × d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule. When accounting for the calculation of intended cumulative dose 3 days should be added to the date of last dose to reflect the protocol allowed window for dosing. When deriving actual dose administered the volumes before and after infusion will also be considered.

4.8.1.2 Presentation

Duration of exposure to study interventions (AZD0171, durvalumab, or standard of care chemotherapy) in months (and cycles) will be summarised by descriptive statistics and by frequency. Dose intensity will be summarised by descriptive statistics. Exposure to study interventions, ie, total amount of study drug received will be listed for all participants. Exposure swimmer plot(s) will be produced, with a line presented for each participant to display relevant exposure and disposition details.

Dosing deviations for study interventions (AZD0171, durvalumab, or standard of care chemotherapy) will be summarised with reasons for deviations for the following categories: delays, reductions, and interruptions. The frequency counts and percentage of the number of participants with reductions and/or interruptions and total count per participant are summarised. The frequency counts and percentage of the number of participants with dosing delays and total count dose delays per participant are summarised.

4.8.2 Adverse Events

4.8.2.1 Definitions and Derivations

An AE is the development of any untoward medical occurrence in a patient or clinical study participant 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 (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

The MedDRA (using the latest agreed MedDRA version) will be used to code the AEs. Adverse events are graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE; using the CTCAE version referenced in the CSP).

Adverse events are defined as treatment emergent if they onset or worsen (by investigator report of a change in intensity/severity), during the treatment phase until the last dose of any study intervention or the safety follow-up period, but prior to subsequent cancer therapy. Worsening is determined by comparison with the pre-treatment severity of the AE recorded closest to the start of dosing.

AEs with a missing start time which occur on the same day as first IP administration will be reported as treatment emergent. Note that the treatment emergent phase includes the on treatment and safety follow-up periods.

When assigning AEs to the relevant phase of the study the following rules apply, as agreed with the study team:

- Pre-treatment phase: Prior to the first administration of study treatment.
- On treatment phase: On or after the first dose of study treatment up to 14 days after the last dose of study treatment or up to the day prior to the start of subsequent therapy, whichever comes first.

- Follow-up phase: After more than 14 days after last dose of study treatment or once subsequent cancer therapy is started, whichever is earlier.

When assigning AEs as treatment emergent the following rules apply, as agreed with the study team:

- Pre-treatment emergent: All AEs with a start date after signing the informed consent form (ICF), prior to the first administration of study treatment that do not subsequently go on to worsen during the time considered as treatment emergent.
- Treatment emergent: All AEs (starting or worsening) on or after the first dose of study treatment and within 90 days after the last dose of study treatment or up to the day prior to the start of subsequent therapy, whichever comes first.
- Follow-up: All AEs starting more than 90 days after last dose of study treatment or once subsequent cancer therapy is started, whichever is earlier.

Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the safety of the participant.

Adverse Events of Special Interest and Immune Mediated Adverse Events

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of study intervention. The list of AESIs for AZD0171 is presented in Section 8.3.6.1 of the CSP.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids and other immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune mediated AE (imAE) is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. The list of AESIs/imAEs for durvalumab is presented in Section 8.3.6.2 of the CSP.

All imAEs for AZD0171 and Durvalumab are programmatically identified using the algorithm detailed in the AZ Durvalumab Tremelimumab imAE Charter. The algorithm defines imAEs as any AESI that received imAE treatment for/during the event, where imAE treatment includes:

- Systemic steroid therapy
- Other immunosuppressants, and/or
- Endocrine treatment, which includes standard endocrine supplementation as well as treatment of symptoms resulting from endocrine disorders

Time to onset of AESI/imAE is defined as start date of the event – date of first dose of IP for the first relevant event experienced by each participant within each IP, AESI category/sub-category and PT. For treatment-emergent events that started prior to date of first dose and worsened on-treatment, the date of worsening will be used in place of the event start date. Time to resolution of AESI and imAE is defined as date of event resolution – start date of event for the worst AESI/imAE for each participant within each IP, AESI category/sub-category and PT, where the worst event is defined as the first event with the highest toxicity grade for each participant which was resolved. In cases where multiple events meet the worst event criteria, the event with the longest duration will be taken as the worst event.

More information regarding AESIs can be found in the protocol. Other categories may be added, or existing terms may be modified as necessary. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to DBL to ensure any further terms not already included are captured within the categories. Preferred terms used to identify AESI is listed before DBL.

4.8.2.2 Presentation

Safety data, including AEs and SAEs, will be summarised based on the safety analysis set. All AEs reported in the treatment-emergent phase will be considered treatment-emergent AEs (TEAEs) and will be summarised and listed. Pre-treatment AEs and off-treatment AEs will also be listed.

Treatment Emergent Adverse Events are counted once for each participant for calculating percentages of participants experiencing TEAE. In addition, if the same TEAE occurs multiple times within a particular participant, the highest severity and level of relationship observed will be reported. For tables by MedDRA SOC and PT, participants with multiple TEAEs are counted once for each SOC/PT. Summary information (the number and percent of participants) by SOC and PT will be tabulated for:

- All AEs
- All AEs possibly related to AZD0171 (as determined by the reporting investigator)
- All AEs causally related to durvalumab (as determined by the reporting investigator)
- All AEs causally related to gemcitabine (as determined by the reporting investigator)
- All AEs causally related to nab-paclitaxel (as determined by the reporting investigator)
- AEs by maximum CTCAE grade
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, possibly related to AZD0171 (as determined by the reporting investigator)
- AEs with CTCAE grade 3 or higher, possibly related to durvalumab (as determined by the reporting investigator)
- AEs with CTCAE grade 3 or higher, possibly related to gemcitabine (as determined by the reporting investigator)
- AEs with CTCAE grade 3 or higher, possibly related to nab-paclitaxel (as determined by the reporting investigator)
- AEs leading to discontinuation of AZD0171
- AEs leading to discontinuation of durvalumab

- AEs leading to discontinuation of gemcitabine
- AEs leading to discontinuation of nab-paclitaxel
- AEs leading to discontinuation of AZD0171, possibly related to study AZD0171 (as determined by the reporting investigator)
- AEs leading to discontinuation of durvalumab, possibly related to study durvalumab (as determined by the reporting investigator)
- AEs leading to discontinuation of gemcitabine, possibly related to study gemcitabine (as determined by the reporting investigator)
- AEs leading to discontinuation of nab-paclitaxel, possibly related to study nab-paclitaxel (as determined by the reporting investigator)
- AEs leading to dose reduction of gemcitabine
- AEs leading to dose reduction of nab-paclitaxel
- AEs leading to interruption of AZD0171
- AEs leading to interruption of durvalumab
- AEs leading to interruption of gemcitabine
- AEs leading to interruption of nab-paclitaxel
- AEs leading to dose modification of AZD0171
- AEs leading to dose modification of durvalumab
- AEs leading to dose modification of gemcitabine
- AEs leading to dose modification of nab-paclitaxel
- SAEs leading to hospitalisation
- SAEs with outcome of death

The number and percent of participants will be summarised for:

- AEs of special interest and Immune mediated AEs for each IP, where IP includes AZD0171 and Durvalumab Infusion reaction AEs

An overall summary table of the number and percentage of participants experiencing each category of adverse event will be produced, as well as an overall summary of the number of events in each category. Summary statistics showing the time to onset of the first AE will also be presented. For treatment-emergent events that worsened on-treatment, the date of worsening will be used in place of the event start date.

Details of any deaths will be summarised and listed for all participants. Adverse events leading to death will also summarised.

Additionally, summary information (number and percent of participants) may be presented for AEs related to COVID-19. A listing may be provided for participants with AEs with confirmed/suspected COVID-19. If there are no participants with COVID-19, these tables and listings will not be required.

Serious Adverse Events

SAEs will be summarised as described above for the TEAEs.

Adverse Events of Special Interest and Immune Mediated Adverse Events

Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI grouping. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

Summaries of the above-mentioned grouped AE categories will include number and percentage of participants who have:

- All AESIs and imAEs presented by event outcome
- All AESIs and imAEs for AZD0171 causally related to AZD0171 (as determined by the reporting investigator)
- All AESIs and imAEs for Durvalumab causally related to Durvalumab (as determined by the reporting investigator)
- All AESIs and imAEs for AZD0171 leading to discontinuation of AZD0171
- All AESIs and imAEs for Durvalumab leading to discontinuation of Durvalumab.

Summary tables of AESI will be produced. The number and percentage of participants experiencing any of the specified terms will be presented overall and by maximum CTCAE grade. A summary of duration of high dose steroids use for AESIs by drug and AESI

category will also be presented. Summary statistics showing the time to onset and resolution of the first AESI and imAE will also be presented. Time to resolution will be repeated for only Grade 2+ events, with both time to onset and resolution repeated for only Grade 3+ events.

4.8.3 Clinical Laboratory: Blood Samples

4.8.3.1 Definitions and Derivations

Laboratory tests are grouped according to chemistry and haematology. The following laboratory variables will be collected:

Table 6: Laboratory safety variables

Clinical Chemistry (Serum or Plasma)	Haematology/Coagualtion
Albumin	Absolute (or differential, %) basophil count
ALP	Absolute (or differential, %) eosinophil count
ALT	Absolute (or differential, %) lymphocyte count
Amylase	Absolute (or differential, %) monocyte count
AST	Absolute (or differential, %) neutrophil count
Bicarbonate	aPTT
B type	Haematocrit
B type natriuretic peptide (BNP)[a]	Hb
BUN or Urea depending on local practice	INR
Calcium (total)	Platelet count
CA19-9*	Prothrombin
Chloride	WBC
Creatinine	
C-reactive protein	
Creatinine clearance (Cockcroft-Gault)	
Gamma glutamyl transpeptidase	
Glucose	
Lactate dehydrogenase	
Lipase	
Magnesium	
Phosphorus	
Potassium	
Sodium	
Total Bilirubin (A direct bilirubin should be obtained if total bilirubin is > ULN)	

Table 6: Laboratory safety variables

Clinical Chemistry (Serum or Plasma)	Haematology/Coagualtion
Total Protein	
Troponin[a]	
TSH	
T3 (reflex)	
T4 (reflex)	
Uric acid	

[a] Safety run-in participants only at baseline.
Note for serum/plasma chemistry: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.
ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; BUN = blood urea nitrogen; CA19-9 = carbohydrate antigen 19-9; Hb = haemoglobin; INR = international normalised ratio; T3 = Free tri-iodothyronine; T4 = free thyroxine; TSH = thyroid stimulating hormone; ULN = upper limit of normal; WBC = white blood cell
*CA19-9 will be analysed and presented as part of PD endpoint.

Listings will be provided for all laboratory results. Laboratory parameters will be assessed at baseline as well as throughout the study.

For chemistry and haematology parameters, laboratory abnormalities with toxicity grades according to the NCI CTCAE version 5.0 will be derived.

Change from baseline in haematology and clinical chemistry endpoints will be calculated for each post-dose visit. The change in each laboratory parameter from baseline to each post-baseline visit will be summarised graphically. Common Terminology Criteria (CTC) grade will be calculated at each visit. Maximum post-baseline CTC will also be calculated. Absolute values will be compared to the local laboratory reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings.

Liver Function Parameters

Participants with elevated post-baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin that fall into these categories will be identified. Number and percentage of these participants will be tabulated. The summaries will be presented based on categories of the liver function parameters below:

Liver Function Parameters	Category
ALT	• $< 3 \times$ ULN • $\geq 3 \times$ – $< 5 \times$ ULN

Liver Function Parameters	Category
	• ≥ 5 × – < 10 × ULN • ≥ 10 × ULN
AST	• < 3 × ULN • ≥ 3 × – < 5 × ULN • ≥ 5 × – < 10 × ULN • ≥ 10 × ULN
Total bilirubin	• < 2 × ULN • ≥ 2 × ULN
Potential Hy's law	• (AST ≥ 3 × ULN or ALT ≥ 3 × ULN) and (BILI ≥ 2×ULN)[a]

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BILI = total bilirubin; ULN = upper limit of normal range.
a It includes all participants who have ALT or AST ≥ 3 x ULN andBILI ≥ 2 x ULN, and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in BILI.

Assessment of Nephrotoxicity

Creatinine clearance rate (CCr) is calculated using serum creatinine and the Cockcroft-Gault formula to estimate glomerular filtration rate (GFR). Baseline and "worst-case" on treatment CCr value will be categorised for the following categories:

- Normal: ≥ 90 mL/min
- Mild Impairment: ≥ 60 − < 90 mL/min
- Moderate Impairment: ≥ 30 − < 60 mL/min
- Severe Impairment: ≥ 15 − < 30 mL/min
- Kidney Failure: < 15 mL/min

4.8.3.2 Presentations

Laboratory abnormalities occurring from the start of study intervention administration to the last assessment on study will be presented. Worst toxicity grade, rates of grade 3 to 4 toxicity, and grade shifts of two or more from baseline to the maximum grade will be presented. Summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate. Laboratory parameters that cannot be graded via NCI CTCAE will be summarised with frequencies of post-baseline laboratory values categorized as low (L), normal (N), or high (H) using laboratory normal ranges compared to baseline. Clinically significant (as assessed by the investigator) laboratory abnormalities will be recorded in the

eCRF as AEs. Blood sample, including liver parameters analysis, will be based on the safety analysis set.

Liver Function Parameters

Individual participant data where elevated ALT or AST plus total bilirubin fall into the "Potential Hy's law" will be listed.

Assessment of Nephrotoxicity

Shift tables from baseline to "worst-case" on treatment CCr value will be provided.

4.8.4 Clinical Laboratory: Urinalysis

4.8.4.1 Definitions and Derivations

The following urinalysis will be summarised:

Table 7: Urinalysis variables

Appearance and colour
Bilirubin
Blood (microscopic examination will be performed only if the results of the urinalysis dipstick evaluation are positive)
Glucose
Ketones
pH
Protein
Specific gravity

Listings will be provided for all laboratory results including urinalysis. Urinalysis will be assessed at baseline (screening), as clinically indicated during the study intervention period, at the end-of-treatment and Day 28 follow-up.

Change from baseline in urinalysis endpoints will be calculated for each post-dose visit. Common Terminology Criteria grade will be calculated at each visit. Maximum post-baseline CTC will also be calculated. Absolute values will be compared to the local laboratory reference range and classified as L (below range), N (within range or on limits of range), and H (above range). All values classified as high or low will be flagged on the listings.

4.8.4.2 Presentations

Laboratory abnormalities occurring from the start of study intervention administration to the last assessment on study will be presented. Worst toxicity grade, rates of grade 3 to 4 toxicity, and grade shifts of two or more from baseline to the maximum grade are presented. Summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate. Laboratory parameters that cannot be graded via NCI CTCAE will be

summarised with frequencies of post-baseline laboratory values categorized as L, N, or H using laboratory normal ranges compared to baseline. Urinalysis will be based on the safety analysis set.

4.8.5 Other Laboratory Evaluations

4.8.5.1 Definitions and Derivations

Lipid panel assessments (total cholesterol and triglyceride), pregnancy tests (urine or serum), and COVID-19 test will be performed according to SoA.

4.8.5.2 Presentations

Lipid panel assessments, pregnancy and COVID-19 data will be listed.

4.8.6 Vital Signs

4.8.6.1 Definitions and Derivations

Vital signs (ideally taken prior to any blood draws or other procedures) will be measured in a supine or semi-recumbent position after 10 minutes rest and will include pulse rate, blood pressure (systolic and diastolic), and temperature.

4.8.6.2 Presentations

Vital signs summaries will be presented for participants in the safety analysis set. Vital signs will be assessed at baseline and throughout the study according to SoA. Vital signs will be summarised by study visit using descriptive statistics for the value of the parameters and the changes from baseline. Absolute values and change from baseline for vital signs data at each timepoint will be presented using box plots. Vital signs will be listed.

4.8.7 Electrocardiogram

4.8.7.1 Definitions and Derivations

Electrocardiogram parameters will be assessed at baseline as well as throughout the study. Electrocardiogram parameters include:

- PR interval (time between onset of the P-wave and onset of the QRS complex),
- RR interval (time between R-waves),
- QRS duration (time from the onset to the end of the QRS complex),
- QT interval (time from the onset of the QRS complex to the end of the T-wave),
- QTcB interval (corrected QT interval using Bazett’s correction formula),
- QTcF interval (corrected QT interval using Fridericia’s correction formula).

The QTcF is considered as the primary correction method to assess participants cardiac safety. All ECGs will be obtained in triplicate (three reads at least 1 minute apart, all within a 5-minute time period). For triplicate ECGs, the mean of the three ECG assessments will be used to determine the value at that time point. Baseline of ECG is the mean of last three ECG assessments prior to first dose. If only two ECG assessments prior to first dose are available, then take the average of these last two ECG assessment prior to first dose as baseline of ECG; if only one ECG assessments prior to first the dose is available, then take the last one ECG assessment prior to the first dose as baseline of ECG.

From these resting 12-lead ECGs values of the QT and RR intervals, the QT interval corrected for heart rate using Fridericia's correction (QTcF) will be derived using the following formula:

- QTcF = QT/RR^ (1/3) where RR is in seconds

The values of QTcF (milliseconds) will be re-derived from the values of RR and QT during the creation of the reporting database.

The notable ECG interval values while on treatment are:

- Maximum QTcF intervals > 450 milliseconds, > 480 milliseconds, and > 500 milliseconds.
- Maximum changes from baseline in QTcF > 30, >60, and > 90 milliseconds.

4.8.7.2 Presentations

Electrocardiogram parameters will be summarised using descriptive statistics by visit and change from baseline in ECG endpoints calculated for each post-dose visit. Absolute values and change from baseline for ECG data at each timepoint will be presented using box plots. Electrocardiogram parameters will be listed.

The number and percentage of participants having notable ECG interval values while on treatment will be summarised.

4.8.8 Anti-Drug Antibodies against AZD0171 and/or durvalumab in serum

4.8.8.1 Definition and Derivations

Detectable ADAs against AZD0171 and/or durvalumab in serum will be measured as per the SoA in Appendix D to assess the immunogenicity of AZD0171 and/or durvalumab.

4.8.8.2 Presentations

Immunogenicity results will be listed for each participant and summarised for the immunogenicity analysis set. The impact of ADAs on PK, Pharmacodynamic, and safety will be assessed, if data allow. Number and percentage of participants in the following categories will be provided:

- Anti-drug antibody positive at baseline and/or post-baseline visits. The percentage of these participants in a population is known as ADA prevalence.
- ADA positive post-baseline and positive at baseline.
- ADA positive post-baseline and not detected at baseline (treatment-induced ADA positive).
- ADA not detected post-baseline and positive at baseline.
- Treatment-boosted ADA positive, defined as baseline positive ADA titre that was boosted to a 4-fold or higher level following drug administration.
- Treatment-emergent ADA positive, defined as the sum of treatment-induced ADA positive and treatment-boosted ADA positive. The percentage of these participants in a population is known as ADA incidence.
- Persistent positive, defined as ADA negative at baseline and having at least two post-baseline ADA positive measurements with ≥ 16 weeks between first and last positive, or an ADA positive result at the last available post-baseline assessment.
- Transient positive, defined as ADA negative at baseline and at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.

All valid assay results from participants who receive any study drug are included in immunogenicity summaries. Blood samples collected outside of the permitted CSP window are summarised at the closest nominal time point that does not already have a value. All participants with titre information are shown in the data listing.

4.8.9 Other Safety Assessments

4.8.9.1 Definitions and Derivations

Echocardiography/Multigated Acquisition

Left ventricular ejection fraction (LVEF) will be measured by Echocardiography (ECHO) or Multigated Acquisition (MUGA) scan at screening and as clinically indicated thereafter as

per the SoA in Appendix D. The overall evaluation (normal/abnormal) and LVEF will be summarised over time. The ECHO/MUGA data (LVEF, heart rate, and overall evaluation) will be listed.

Performance Status

Performance status will be assessed as per the SoA and according to United States ECOG criteria and summarised over time. The ECOG data will be listed.

4.9 Analyses of Pharmacodynamic Endpoints

4.9.1 Assessment of CD8+ T Cell Tumour Infiltration in Tumour Samples at Baseline and On-treatment, and Serum CA19-9

Analyses will be based in the pharmacodynamic analysis set. Descriptive statistics will be presented to describe participant and treatment specific results over time and changes from screening values.

Serum CA19-9 will be analysed similarly to assessment of CD8+ T cell tumour infiltration in tumour samples. The change from baseline values will be summarised.

See Section 3.3.1for definitions of baseline and change from baseline.

4.9.2 Total LIF

Analysis methods for the secondary endpoint total LIF are described in Section 4.10.1 and will be based on the PK analysis set.

4.9.3 CCI

CCI [redacted]

4.10 Analyses of Pharmacokinetic Endpoints

4.10.1 Pharmacokinetic Parameters for AZD0171, Durvalumab, and Chemotherapies and/or their Metabolites

Analyses will be based on the PK analysis set. All PK parameters will be summarised for each analyte by PK Day/Visit using appropriate descriptive statistics.

Plasma PK Parameters

Pharmacokinetic analysis is, where data allow, carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist with approval from the AZ Clinical Pharmacology Scientist (CPS). Nominal sampling times may be used for any agreed interim PK parameter calculations.

For each PK sampling period, plasma concentrations that are non-quantifiable (NQ) from the time of pre-dose sampling (t = 0) up to the time of the first quantifiable concentration is set to a value of zero. After this time point, NQ plasma concentrations are set to Lower limit of quantification (LLOQ) for all concentration profiles. Where two or more consecutive concentrations are NQ at the end of a profile, the profile is deemed to have terminated and therefore any further quantifiable concentrations are set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug. If an entire concentration-time profile is NQ, the profile is excluded from the PK analysis.

Cmax, tmax, and tlast are taken directly from the concentration-time profiles.

Refer to Appendix C for the calculation of PK parameters including Elimination rate constant associated with the terminal phase (λz), AUCinf, AUCtau, and Clearance (CL).

For each analyte, plasma concentrations for each scheduled time-point will be summarised by PK Day/Visit using appropriate descriptive statistics. Individual concentrations with time deviations of greater than 10% from the protocol scheduled time will be used in the PK analysis but will be flagged for exclusion from the summary tables and corresponding figures.

The following descriptive statistics will be presented for plasma concentrations:

- n
- n below lower limit of quantification (LLOQ)
- geometric mean (gmean)
- geometric standard deviation (gSD)
- gmean ± gSD
- geometric coefficient of variation (%) (gCV)
- arithmetic mean of non-log-transformed data (mean)
- standard deviation of non-log-transformed data (Std Dev)

- median
- minimum (min)
- maximum (max)

The gmean is calculated as exp(μ), where μ is the mean of the data on the natural log scale.

The gSD is calculated as exp(σ), where σ is the standard deviation of the data on the natural log scale.

The gCV is calculated as 100 x sqrt[exp(σ^2)-1], where σ is the standard deviation of the data on the natural log scale.

The gmean ± gSD (gmean-gSD and gmean+gSD) are calculated as exp[μ ± σ].

Protocol scheduled times are used to present the PK concentration summary tables and corresponding gmean concentration-time figures.

Handling of Non-Quantifiable Concentrations

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant tables, figures, listings (TFLs). Individual plasma concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR, or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values within PK parameters across all participants are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean, gmean ± gSD and gCV% will be set to NC. The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The gmean, minimum, median, and maximum will be reported as NQ and the gCV% and gmean ± gSD as NC.

- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration or PK parameter (eg, C_{max}) to be summarised. Two observations > LLOQ will be presented as minimum and maximum with the other summary statistics as NC.

PK Parameter Descriptive Statistics

The following descriptive statistics for PK parameters will be presented:

- n, gmean, gmean+gSD, gmean-gSD, arithmetic mean of non-log-transformed data (mean), standard deviation of non-log-transformed data (Std Dev), gCV(%), median, minimum, and maximum.
- Diagnostic Paramters: n, arithmetic mean of non-log-transformed data (mean), standard deviation of non-log-transformed data (Std Dev), median, min, and max.
- tmax, tlast, lambda z upper and lambda z lower: n, median, minimum, and maximum.

Three values are required as a minimum for PK parameters to be summarised. Two values will be presented as a minimum and maximum with the other summary statistics as NC.

If one or more values for a given parameter is zero, then no geometric statistics will be calculated for that parameter and the results for geometric statistics will be set to NA (not applicable).

Pharmacokinetic parameter Listings

All reportable PK parameters, including individual diagnostic and lambda z related parameters, will be listed for each subject by PK Day/Visit, for each analyte separately.

Graphical presentation of PK data

All mean (arithmetic mean and/or gmean) concentration plots or combined plots showing all participants will be based on the PK analysis set. Individual concentration plots by participants will be based on the Safety analysis set. Scatter plots for individual PK parameters versus Treatment presenting both summary parameter data and individual

participants parameter data for each Treatment including only participants in the PK analysis set will be presented.

For consistency, the plasma concentration values used in the mean (arithmetic mean and/or gmean) data graphs will be those given in the descriptive statistics summary table for each time point.

For gmean concentration-time plots, NQ values will be handled as described for the descriptive statistics; if the geometric mean is NQ, the value plotted will be zero for linear plots and missing for semi-logarithmic plots. Any gmean ± gSD error bar values that are negative will be truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

For individual plots, plasma concentrations which are NQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations will be regarded as missing.

Data permitting, the following figures will be presented as appropriate:

- Figures for the mean (gmean) plasma concentration-time data (with ± Std Dev error bars) will be presented on both linear and semi-logarithmic scales using scheduled post-dose time
- Individual participant plasma concentration-time data will be graphically presented on both linear and semi-logarithmic scales using actual time post-dose as:
    - By-participant with all and/or selected PK Days for the same participant overlaid on the same plot
- Individual and summary PK parameter data will be graphically presented on scatter plots of the PK parameter value

Precision and Rounding Rules for PK Data

Pharmacokinetic Concentration Data

PK concentration data listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to three significant figures) and against the same units as received.

PK concentration descriptive statistics will be presented as four significant figures with the exception of the minimum, and maximum which will be presented as three significant figures and n and n < LLOQ which will be presented as integers.

Pharmacokinetic Parameter Data

Pharmacokinetic parameter listings will be presented to three significant figures with the exception of:

- Cmax: present to the same number of significant figures as received from the bioanalytical laboratory
- tmax, tlast, lambda z lower and lambda z upper: present as received in the data, usually to two decimal places
- lambda z N: present as an integer (no decimals)

The descriptive statistics for PK parameter data are presented to four significant figures with the exception of the minimum and maximum which are presented to three significant figures apart from the following:

- tmax and tlast: present as received in the data, usually to two decimal places
- number of values (n): present as an integer

4.10.2 Drug-drug Interaction Risk between Chemotherapy and AZD0171 and/or Durvalumab

These analyses will be described separately from the SAP and presented separately from the main CSR.

5 INTERIM ANALYSIS

An interim analysis will be performed when approximately 40 evaluable participants have been dosed and have had the opportunity to complete two post-baseline scans (see Section 3.2). For justification of sample size of the interim analysis, please refer to the sample size Section 3.3.6.

In addition to the ORR, the interim analysis will include participant disposition and key safety endpoints.

6 REFERENCES

C. J. Clopper, E. S. Pearson, The use of confidence or fiducial limits illustrated in the case of the binomial, Biometrika. 1934; 26:404–416.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guidelines (version 1.1). European Journal of Cancer. 2009; 45:228-47.

Frewer P, Mitchell P, Watkins C, and Matcham J. Decision-making in early clinical drug development. Pharma Statist. 2016; 15:255-263.

7 APPENDICES

Appendix A RECIST v1.1

Derivation of RECIST v1.1 Visit Responses

For all participants, the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) tumour response data is used to determine each participant's visit response according to RECIST v1.1. It is also used to determine if and when a participant has progressed in accordance with RECIST v1.1and their best overall response to study intervention.

Baseline radiological tumour assessments are performed no more than 28 days before the start of study intervention and ideally as close as possible to the start of study intervention. Tumour assessments are performed every 8 weeks (± 1 week) following the start of study intervention for the first 48 weeks, then every 12 weeks (± 1 week), until disease progression or end of survival follow-up, whichever comes first.

If an unscheduled assessment is performed, and the participant has not progressed, every attempt is made to perform the subsequent assessments at their scheduled visits. This schedule is followed in order to minimise any unintentional bias caused by some participants being assessed at a different frequency than other participants.

From the investigator's review of the imaging scans, the RECIST v1.1 tumour response data is used to determine each participant's visit response according to RECIST v1.1. At each visit, participants are programmatically assigned a RECIST v1.1 visit response of Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD), using the information from target lesions (TLs), non-target lesions (NTLs) and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a participant has had a tumour assessment that cannot be evaluated then the participant is assigned a visit response of not evaluable (NE), (unless there is evidence of progression in which case the response is assigned as PD).

Please refer to Table 1Target Lesion Visit Responses (RECIST v1.1)of the Appendix for the definitions of CR, PR, SD, and PD.

RECIST v1.1 outcomes (ie, progression-free survival [PFS], objective response rate [ORR], etc.) are calculated programmatically for the site investigator data (see last section of this Appendix) from the overall visit responses.

Target Lesions – Site Investigator Data

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD), (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements. A participant can have a maximum of five measurable lesions recorded at baseline with a maximum of two lesions per organ (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as target lesions (TLs). If more than one baseline scan is recorded, then measurements from the one that is closest and prior to first dose is used to define the baseline sum of TLs. It is the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In which circumstance the next largest lesion, which can be measured reproducibly, is selected.

All other lesions (or sites of disease) not recorded as TL are identified as non-target lesions (NTLs) at baseline. Measurements are not required for these lesions, but their status are followed at subsequent visits.

Note: For participants who do not have measurable disease at entry (ie, no TLs) but have non-measurable disease, evaluation of overall visit response is based on the overall NTL assessment and the absence/presence of new lesions (see section below for further details). If a participant does not have measurable disease at baseline, then the TL visit response is not applicable (NA).

Table 1 Target Lesion Visit Responses (RECIST v1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all target lesions (TLs). Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5 mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Visit Responses	Description
Not evaluable (NE)	Only relevant in certain situations (ie, if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	No TLs are recorded at baseline.

Rounding of TL Data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum are rounded to one decimal place. before assigning a TL response. For example, 19.95% is rounded to 20.0% but 19.94% is rounded to 19.9%.

Missing TL Data

For a visit to be evaluable then all TL measurements are recorded. However, a visit response of PD is still assigned if any of the following occurred:

- A new lesion is recorded,
- An NTL visit response of PD is recorded,
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5 mm, from nadir even assuming the non-recorded TLs have disappeared.

Note: The nadir can only be taken from assessments where all the TLs had a LD recorded.

If the TL visit response is not recorded as PD, then the TL visit response is NE.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

If all TL measurements are missing, then the TL visit response is NE. Overall visit response is also NE, unless there is a progression of non-TLs or new lesions, in which case the response is PD.

Lymph Nodes

For lymph nodes, if the size reduces to < 10 mm then these are considered non-pathological. However, a size is still given, and this size is still used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10 mm and all other TLs are 0 mm

then although the sum may be > 0 mm the calculation of TL response should be over-written as a CR.

Target Lesions Visit Responses Subsequent to CR

Only CR, PD, or NE can follow a CR. If a CR has occurred, then the following rules at the subsequent visits must be applied:

- If all lesions meet the CR criteria (ie, 0 mm or < 10 mm for lymph nodes) then response is set to CR irrespective of whether the criteria for PD of TL is also met, ie, if a lymph node short axis increases by 20% but remains < 10 mm.
- If some lesion measurements are missing but all other lesions meet the CR criteria (ie, 0 mm or < 10 mm for lymph nodes) then response is set to NE irrespective of whether the criteria for PD of TL is also met ie, if a lymph node short axis increases by 20% but remains < 10 mm.
- If not, all lesions are missing, and those that are non-missing do not meet the CR criteria (ie, a pathological lymph node selected as TL has short axis ≥ 10 mm or the reappearance of previously disappeared lesion), then response is set to PD.
- If all lesions are missing the response is set to NE.

Target Lesions too Big to Measure

If a TL becomes too big to measure this is indicated in the database and a size ('*x*') above which it cannot be accurately measured is recorded. If using a value of *x* in the calculation of TL response does not give an overall visit response of PD, then this is flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD remains in the vast majority of cases.

Target Lesions too Small to Measure

If a TL becomes too small to measure, then this is indicated as such on the case report form and a value of 5 mm is entered into the database and used in TL calculations. However, a smaller value is used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response of PD results (at a subsequent visit) then this is reviewed by the study team blinded to treatment assignment.

Irradiated Lesions/Lesion Intervention

Previously irradiated lesions (ie, lesion irradiated prior to entry into the study) are recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation/palliative surgery/embolization but note this does not include protocol specified biopsies), are handled in the following way. Once a lesion has had intervention then it is treated as having intervention for the remainder of the study noting that an intervention most likely shrinks the size of tumours:

- Step 1: The diameters of the TLs (including the lesions that have had intervention) are summed and the calculation is performed in the usual manner. If the visit response is PD, this remains as a valid response category.
- Step 2: If there is no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing. If PD has not been assigned, then the visit response is set as NE.

At subsequent visits, the above steps are repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention are treated as missing.

Scaling for Sensitivity Analysis

Scaling is applicable only for the sensitivity analysis for irradiated lesions/lesion intervention.

For the sensitivity analysis, if > 1/3 of TL measurements are missing (because of intervention) then the TL response is NE, unless the sum of diameters of non-missing TL would result in PD (ie, if using a value of 0mm for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥ 5 mm from nadir).

If ≤ 1/3 of the TL measurements are missing (because of intervention) then the results are scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters) and this is used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to their nadir sum of diameters, excluding the lesions with missing measurements.

Example of Scaling

Lesion 5 is missing at the follow-up visit; the nadir TL sum including lesions 1-5 was 74 mm.

The sum of lesions 1-4 at the follow-up is 68 mm. The sum of the corresponding lesions at the nadir visit is 62 mm.

Scale up as follows to give an estimated TL sum of 81 mm:

68 x 74 / 62 = 81 mm

Complete Response is not allowed as a TL response for visits where there is missing data. Only PR, SD, or PD (or NE) is assigned as the TL visit response in these cases. However, for visits with ≤ 1/3 lesion assessments not recorded, the scaled-up sum of TLs diameters are included when defining the nadir value for the assessment of progression.

Irradiated Lesions/Lesion Intervention for Sensitivity Analysis using Scaling

For the sensitivity analysis, the irradiated lesions/lesion intervention steps above are replaced with the following three steps:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) are summed and the calculation is performed in the usual manner. If the visit response is PD, this remains as a valid response category.

- Step 2: If there is no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling for sensitivity analysis' section. If the scaling results in a visit response of PD, then the participant is assigned a TL response of PD.

- Step 3: If PD has not been assigned, then, if appropriate (ie, if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 are used, and PR or SD then assigned as the visit response. Participants with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or < 10 mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or < 10 mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements, then the visit response is set as NE.

At subsequent visits, the above steps are repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2).

Lesions that Split in Two

If a TL splits in two, then the LDs of the split lesions are summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion are recorded for one of the TL sizes and the other TL size is recorded as 0 mm.

Change in method of assessment of TLs

Computed Tomography, MRI, and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. If a change in method of assessment occurs, between CT and MRI this is considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (eg, CT changes to clinical examination or vice versa), any affected lesions are treated as missing.

Non-target Lesions and New Lesions – Site Investigator Data

At each visit, the investigator is to record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Non-Target Lesions response is derived based on the investigator's overall assessment of NTLs as follows:

Table 2 Non-Target Lesions Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all non-target lesions (NTLs) present at baseline with all lymph nodes non-pathological in size (< 10 mm short axis).
Progressive disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For participants without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if there are no NTLs at baseline.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in

TLs, the overall tumour burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions are also recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

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

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

New lesions are identified via a Yes/No tick box. The absence and presence of new lesions at each visit are listed alongside the TL and NTL visit responses.

A new lesion indicates progression, so the overall visit response is PD irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank, this is not evidence that no new lesions are present but should not overtly affect the derivation.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and is not included in any assessment of NTLs.

Participants with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

Overall Visit Response – Site Investigator Data

Table 3 Overall visit responsesdefines how the previously defined TL and NTL visit responses are combined with new lesion information to give an overall visit response.

Table 3 Overall visit responses

Target	Non-target	New Lesions	Overall Visit Response
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**

Target	Non-target	New Lesions	Overall Visit Response
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-PD	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**
NA	NA	No (or NE)	**NED**

CR = Complete Response; NA = Not Applicable; NE = Not Evaluable; NED = Non-evaulable Disease;PD = Progressive Disease; PR = Partial response; SD = Stable Disease;

Appendix B Dosing Considerations for Study Interventions

Participants who Permanently Discontinue During a Dose Interruption

If a participant permanently discontinues study intervention during a dose interruption, then the date of last administration of study intervention recorded on the Discontinuation of Investigational Product/Additional Drug Case Report Form (CRF) is used in the programming.

Example of Participants who Permanently Discontinued During a Dose Interruption

Dose	Start date	Stop date	Reason for change
300 mg	23/01/11	14/02/11	NA
0 mg	15/02/11	28/02/11	AE (dose interrupted)
200 mg	01/03/11	13/03/11	AE (dose restarted and reduced)
0 mg	14/03/11	15/03/11	AE (dose interrupted)
0 mg	16/03/11		RECIST v1.1 progression (permanently discontinued)

The data is recorded as above on the Exposure CRF. The date of last dose for this participant used in the programming and recorded on the Discontinuation of Investigational Product/Additional Drug CRF module is 13/03/11 and the reason for permanent discontinuation recorded on the Discontinuation of Investigational Product/Additional Drug CRF is an adverse event (AE). This participant has one dose interruption according to the summary tables as the second dose interruption is not included as an interruption.

Appendix C Pharmacokinetic Parameter Derivation

Pharmacokinetic (PK) parameters listed below will be calculated for all analytes (AZD0171, gemcitabine, nab-paclitaxel and metabolite-gemcitabine) unless specified otherwise.

AUCinf	Area under plasma concentration-time curve from zero to infinity (AZD0171 only)
AUClast	Area under the plasma concentration-curve from zero to the last quantifiable concentration
Cmax	Maximum observed plasma (peak) drug concentration
Cmin	Minimum observed plasma drug concentration
Tmax	Time to reach maximum observed concentration
t1/2λz	Terminal elimination half-life
AUCτ	Area under concentration-time curve in the dose interval
Vz/F	Apparent volume of distribution based on the terminal phase (AZD0171 only)
CL/F	Apparent total body clearance (AZD0171 only)
Rac Cmax	Accumulation ratio for Cmax (AZD0171 only)
Rac AUC	Accumulation ratio for AUC (AZD0171 only)
MPCmax	Metabolite to parent ratio based on Cmax (gemcitabine only)
MPAUC	Metabolite to parent ratio based on AUC (gemcitabine only)

The following diagnostic parameters for plasma PK analysis will be listed, but not summarized:

λz lower	Lower (earlier) time used for λz determination
λz upper	Upper (later) time used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
λz	Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve
λzN	Number of data points used for λz determination
Rsq_adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
AUCextr	Extrapolated area under the curve from tlast to infinity (%)

Where there are sufficient data, λz is calculated by log-linear regression of the terminal portion of the concentration-time profiles and t½λz is calculated as ln2/λz. For the

determination of λz, the start of the terminal elimination phase for each participant is defined by visual inspection and is the first time point at which there is no systematic deviation from the log-linear decline in plasma concentrations (t lower). The last point (t upper) is the time of the last quantifiable plasma concentration.

The choice of data points used to estimate λz follows the general guidelines:

- If there is more than one phase, use only observations from the terminal phase.
- In general, a minimum of three quantifiable concentrations are required (n obs ≥ 3) and the recommended duration of time over which λz is evaluated is at least three times the subsequently estimated terminal half-life (t½λz). Where t½λz is estimated over less than three half-lives, the value is flagged in the data listings.
- Include the last quantifiable concentration.
- Include only observations after peak concentration.

For drugs showing multi-phasic decline in plasma concentrations over time, estimation of an effective or alpha half-life (t½) may be derived from λz calculated by log-linear regression of an earlier phase of the concentration-time profile. Estimation of this λz requires a minimum of three quantifiable concentrations, may include the peak concentration observation and has a Rsq adj value of ≥ 0.8 as a measure of good correlation.

AUCs (including AUC, AUClast, AUCτ, AUC(t1-t2)) are calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up, log down). AUC is estimated by AUClast + Clast/λz where Clast is the observed last quantifiable drug concentration.

The minimum requirement for the calculation of AUC is the inclusion of at least three consecutive plasma concentrations above the Lower limit of quantification (LLOQ), with at least one of these concentrations following peak concentration. An exception to the criteria for at least one of the quantifiable concentrations to be following peak concentration may be applied for the calculation of metabolite AUC.

Clearance is determined from the ratio of dose/AUC.

Dose normalised PK parameters for Cmax, AUC, AUClast, and AUC(t1-t2) is determined by dividing the parameter by the dose administered for that PK period.

Appendix D Schedule of Activities

Table 4: Schedule of Activities (Screening)

Procedure	Screening (Day -28 to Day -1)	Details in CSP Section or Appendix of CSP
Written informed consent/ assignment of PID number[a]	X	5.1
Demographics (age, race, and ethnicity)	X	8
Medical history (including smoking and prior therapies)	X	8
Verify eligibility criteria	X	5.1 and 5.2
Physical examination (full)	X	8.2.1
Height and weight	X	8.2.1
Vital signs	X	8.2.2
Resting 12-Lead ECG (in triplicate all within a 5 minute period)	X	8.2.3
ECOG performance status	X	8.2.5
ECHO/MUGA	X	8.2.4
Assessment of AEs/SAEs	X	8.3
Concomitant medications	X	8
Local Laboratory Assessments		
Clinical chemistry	X	8.2.6
Haematology	X	8.2.6
Thyroid function (TSH, free T4, optional free T3)	X	8.2.6
CA19-9	X	8.2.6
C-reactive protein	X	8.2.6
Lipid panel	X	8.2.6
Urinalysis	X	8.2.6
Pregnancy test (serum; WOCBP only)[b]	X	8.2.6

Coagulation parameters (aPTT and INR)[c]	X	8.2.6
SARS-CoV-2 diagnostic test	X	8.2.6
Hepatitis B, C, and A; HIV-1 and HIV-2 virology	X	8.2.6
BNP[d]	X	8.2.6
Troponin[d]	X	8.2.6
Disease Evaluation[e]		
Contrasted CT (preferred over non-contrasted CT, preferred over MRI) of the chest, abdomen and pelvis	X	8.1.1 and Appendix D
MRI (preferred) scan of brain if clinical concern for brain metastases	X	8.1.1 and Appendix D
CCI Evaluation (Central Laboratory)		
CCI	X	8.5.3.4
CCI	X	8.5.3.3
CCI	X	8.5.3.2
CCI	X	8.5.3.2
CCI	X	8.6.1
CCI	X	8.5 and Appendix A 3
CCI	X	8.7 and Appendix G

a Informed consent must be obtained within 28 days prior to initiation of study intervention and before any study-related procedures are conducted.

b Women of childbearing potential only.

c If INR is not available, the sites may substitute a prothrombin time.

d Safety run-in participants only at baseline.

e Disease assessments obtained prior to informed consent as part of standard-of-care treatment but within 28 days of first dose may be submitted instead if the collection meets the study requirements, otherwise repeat scans should be obtained.

f All participants must consent to providing CCI specimens. If CCI tissue is not available within 3 months of signed informed consent or if the CCI tissue is not sufficient, then participants must consent to and provide a CCI as part of screening prior to first dose of study intervention (see Section 8.5.3.4 of CSP). CCI or recently performed standard of care diagnostic biopsy during metastatic stage is an eligibility requirement for CD8+ assessment. If diagnostic biopsy sample is not available, the investigator may perform a CCI based on risk assessment and only if considered safe to perform. It is strongly recommended that shipment of CCI specimens to the central laboratory test facility should occur within 2 weeks of signed ICF.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = beta-human chorionic gonadotropin; CA19-9 = carbohydrate antigen 19-9; CSP = clinical study protocol; CT = computed tomography; CCI ; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; CCI ; HIV-1 = human immunodeficiency virus-1; ICF = informed consent form; INR = international normalised ratio; MUGA = multigated acquisition; MRI = magnetic resonance imaging; PID = participant identification; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; T3 = triiodothyronine; T4 = thyroxine; THS = thyroid stimulating hormone; WOCBP = woman of childbearing potential.

Table 5: Schedule of Activities (Treatment Period)

Procedure	Treatment Period/Cycle Day																		Details in CSP Section or Appendix of CSP
Window	D -3[a]	28-day Cycle: Window for Each Assessment is ± 3 day after Cycle 1 Day 1, Window for Tumour Assessment ±7 days																	
Cycle number	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6 and Subsequent Cycles			
Cycle number and cycle day	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C3 D8	C3 D15	C4 D1	C4 D8	C4 D15	C5 D1	C5 D8	C5 D15	C6 D1	C6 D8	C6 D15	
Symptom directed physical/oral examination[b]	X			X			X			X			X			X			8.2.1
Weight	X			X			X			X			X			X			8.2.1
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.2
Electrocardiogram (ECG)[d]	X		X			X				X									8.2.3
ECOG performance status	X			X			X			X			X			X			8.2.5
ECHO/MUGA	As clinically indicated.																		8.2.4
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8
Local Laboratory Assessments[e]																			
Clinical chemistry	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.6
Haematology	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.6
Thyroid function (TSH, free T4, optional free T3)	X[f]			X			X			X			X			X			8.2.6
CA19-9	X[f]			X			X			X			X			X			8.2.6

Procedure	Treatment Period/Cycle Day																		Details in CSP Section or Appendix of CSP
Window	**D -3[a]**	**28-day Cycle: Window for Each Assessment is ± 3 day after Cycle 1 Day 1, Window for Tumour Assessment ±7 days**																	
Cycle number	**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6 and Subsequent Cycles**			
Cycle number and cycle day	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D8**	**C3 D15**	**C4 D1**	**C4 D8**	**C4 D15**	**C5 D1**	**C5 D8**	**C5 D15**	**C6 D1**	**C6 D8**	**C6 D15**	
Pregnancy test (urine or serum; WOCBP only)[g]	X			X			X			X			X			X			8.2.6
Urinalysis	As clinically indicated.																		8.2.6
Coagulation parameters (aPTT and INR)	As clinically indicated. See footnote[h]																		8.2.6
Disease Evaluation																			
Disease assessments scans (Contrasted CT [preferred over non-contrasted CT, preferred over MRI])[i]	Acquire scans at the end of cycle (Day 28) Q8W ± 7 days for the first 48 weeks and then Q12W ± 7 days thereafter relative to the date of first dose until unequivocal radiological/clinical progression or start of post treatment cancer therapy, unless not clinically feasible. Imaging schedule should be followed as best as possible and/or as clinically feasibly.																		8.1.1 and Appendix D
Central Laboratory[e]																			
Serum for AZD0171 ADA[j]	X		X	X		X	X			X			X			X			8.5.2
Serum for durvalumab ADA[j]	X			X			X			X			On Day 1 Q3 cycles from C5						8.5.2
CCI [redacted]				X		X	X												8.5.3.3
CCI [redacted]			X	X			X						On Day 1 Q3 cycles from C5						8.5.3.2
CCI [redacted]			X	X			X						On Day 1 Q3 cycles from C5						8.5.3.2

Procedure	Treatment Period/Cycle Day																		Details in CSP Section or Appendix of CSP
Window	**D -3[a]**	**28-day Cycle: Window for Each Assessment is ± 3 day after Cycle 1 Day 1, Window for Tumour Assessment ±7 days**																	
Cycle number	**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6 and Subsequent Cycles**			
Cycle number and cycle day	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D8**	**C3 D15**	**C4 D1**	**C4 D8**	**C4 D15**	**C5 D1**	**C5 D8**	**C5 D15**	**C6 D1**	**C6 D8**	**C6 D15**	
CCI [redacted]			X	X									On Day 1 Q3 cycles from C5						8.6.1
Serum LIF	X																		8.5.3.2
Serum of Total LIF	X	X	X	X	X	X	X	X	X	X	X	X	On Day 1 of every cycle from C5-C11						8.5.3.2
Pharmacokinetics (PK)[k] (See Section 8.5.1 for further details)																			
Plasma for gemcitabine PK	X		X							X		X							8.5.1
Plasma for nab-paclitaxel PK	X		X							X		X							8.5.1
Serum for durvalumab PK	X			X			X			X			On Day 1 Q3 cycles from C5-C11						8.5.1
Serum for AZD0171 PK	X	X	X	X	X	X	X	X	X	X	X	X	On Day 1 of every cycle from C5-C11						8.5.1
On study Biopsies[l]																			
Mandatory on study tumour biopsy							To be collected after the first disease assessment scan during Cycle 3												8.5.3.4
CCI [redacted]	To be collected at disease progression																		8.5.3.4
Treatment Administration (to be given on the same day: AZD0171, durvalumab, and then chemotherapy. See Section 6.2.5)																			6.2.5

Procedure	Treatment Period/Cycle Day																		Details in CSP Section or Appendix of CSP
Window	**D -3[a]**	**28-day Cycle: Window for Each Assessment is ± 3 day after Cycle 1 Day 1, Window for Tumour Assessment ±7 days**																	
Cycle number	**Cycle 1**			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6 and Subsequent Cycles**			
Cycle number and cycle day	**C1 D1**	**C1 D8**	**C1 D15**	**C2 D1**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D8**	**C3 D15**	**C4 D1**	**C4 D8**	**C4 D15**	**C5 D1**	**C5 D8**	**C5 D15**	**C6 D1**	**C6 D8**	**C6 D15**	
AZD0171	X		X	X		X	X		X	X		X	X		X	X		X	6
Durvalumab	X			X			X			X			X			X			6
Gemcitabine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6
Nab-paclitaxel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6

a Up to - 3 days of C1D1.
b Per investigator discretion, dental examination consult may be sought as required for clinically significant findings.
c Vital signs on study intervention days will be measured according to the collection times in Table 9 of the CSP.
d All ECGs will be obtained in triplicate (3 reads at least 1 minute apart, all within a 5-minute time period) (see Table 10 and Table 11 of the CSP for further details).
e Local and Central Laboratories: Assessments will be collected prior to administration of any study intervention. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of any study intervention.
f If screening assessments have been performed within the 3 days prior to Day 1 (Days -3 to -1), then assessment does not need to be performed pre-dose on Day 1. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of the scheduled dose of study intervention.
g Pregnancy test: For women of childbearing potential only. A urine or serum pregnancy test is acceptable, if urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study intervention. Pregnancy test may occur on Cycle 1 Day 1, but results must be available and reviewed by the treating physician or investigator prior to administration of any study intervention.
h Coagulation tests: aPTT and INR – only performed at screening and as clinically indicated. If INR is not available, the sites may substitute a prothrombin time.
i Disease assessments should be performed at every 8 weeks ± 7 days for 1 year and then every 12 weeks ± 7 days until EOT or progressive disease. If post-baseline radiological imaging indicates progressive disease, a separate consent must be signed before the participant may continue study intervention.
j ADA samples should be collected at the same time as PK samples.
k PK samples: PK timepoints will be collected in the first 40 participants that includes 10 to 12 safety run-in participants. Intensive PK timepoints for the safety run-in participants will be collected for AZD0171 and Total LIF PK (Cycle 1 and Cycle 4 Day 1) and chemotherapy (gemcitabine and nab-paclitaxel) PK (Cycle 1 and Cycle 4 Day 15). Detailed PK timepoint(s) for all participants including the safety run-in participants will be collected according to schedules in Table 18 to Table 24 of the CSP.
l Biopsies will be obtained at acceptable risk as judged by the investigator using low-risk procedures.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = beta-human chorionic gonadotropin; C = cycle; CA19-9 = carbohydrate antigen 19-9; CSP = clinical study protocol; CT = computed tomography; CCI ; D = Day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = End of Infusion; EOT = end--of-treatment; Ig = immunoglobulin; imAE = immune mediated adverse event; INR = international normalised ratio; LIF = leukaemia inhibitory factor; MUGA = multigated acquisition; MRI = magnetic resonance imaging; n = visit number; PK = pharmacokinetics; Q2W = every 2 weeks; Q3 = every 3; Q3W = every 3 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = woman of childbearing potential.

Table 6: Schedule of Activities (End of Treatment and Follow-up)

	EOT/ Cycle Day	Follow-up (FUP) Post EOT/ Cycle Day			
Procedure	**Up to Day 14 Post Last Dose**	**Day 28 (FUP-1) (± 7 days) Post Last Dose**	**Day 90 (FUP-2) (± 7 days) Post Last Dose**	**FUP-n Q8W (± 7 days) Starting 20 Weeks Post Last Dose**	**Details in CSP Section or Appendix of CSP**
Clinical Assessments					
Symptom directed physical/oral examination and weight[a]	X	X			8.2.1
Vital signs	X	X	X		8.2.2
Electrocardiogram (in triplicate all within a 5 minute time period)	X				8.2.3
ECOG performance Status	X	X			8.2.5
Assessment of AEs/SAEs	X	X	X		8.3
Concomitant medications	X	X	X		8
Follow-up for survival (telephone contact if visits are discontinued)			X	X	8.1.2
Collection of subsequent anti-cancer treatment			X	X	
Local Laboratory Assessments					
Clinical chemistry	X	X			8.2.6
Haematology	X	X			8.2.6
Thyroid function (TSH, free T4, optional free T3)	X	X			8.2.6
CA19-9	X	X			8.2.6
Urinalysis	X	X			8.2.6
Pregnancy test (urine or serum; WOCBP only)[b]	X				8.2.6

	EOT/ Cycle Day	Follow-up (FUP) Post EOT/ Cycle Day			
Procedure	**Up to Day 14 Post Last Dose**	**Day 28 (FUP-1) (± 7 days) Post Last Dose**	**Day 90 (FUP-2) (± 7 days) Post Last Dose**	**FUP-n Q8W (± 7 days) Starting 20 Weeks**	**Details in CSP Section or Appendix of CSP**
Coagulation parameters (aPTT and INR)	As clinically indicated.				8.2.6
Lipid panel	X	X			8.2.6
Disease Evaluation					
Disease assessment scans (Contrasted CT [preferred over non-contrasted CT, preferred over MRI scan])[c]	Acquire scans Q8W ± 7 days for the first 48 weeks and then Q12W ± 7 days thereafter relative to the date of first dose until unequivocal radiological/clinical progression or start of post treatment cancer therapy, unless not clinically feasible.				8.1.1 and Appendix D
Central Laboratory Assessments					
Serum for AZD0171 ADA	X	X	X		8.5.2
Serum for durvalumab ADA	X	X	X		8.5.2
CCI [redacted]		X			8.5.3.3
CCI [redacted]		X			8.5.3.2
CCI [redacted]		X			8.5.3.2
CCI [redacted]		X			8.6.1
CCI [redacted]					
CCI [redacted]	To be collected at disease progression				8.5.3.4
Pharmacokinetics (PK)					
Serum for AZD0171 PK	X	X	X		8.5.1
Serum for durvalumab PK	X	X	X		8.5.1

a Per investigator discretion, dental examination consult may be sought as required for clinically significant findings.

b Women of childbearing potential only. Urine pregnancy tests will be performed either on-site or at home; the study site will contact the participant by phone to obtain results for tests performed at home. If urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation.

[c] Only for participants who discontinued for reasons other than progressive disease. If post-baseline radiological imaging indicates progressive disease, a separate consent must be signed before the participant may continue treatment.

[d] Biopsies will be obtained at acceptable risk as judged by the investigator using low-risk procedures.

Abbreviations: ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CA19-9 = carbohydrate antigen 19-9; CT = computed tomography; CCI CSP = clinical study protocol; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FUP = follow-up; INR = international normalised ratio; MRI = magnetic resonance imaging; PK = pharmacokinetics; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = woman of childbearing potential.

Signature Page for VV-RIM-02714615 System v3.0
D8151C00001 Statistical Analysis Plan Edition 3

Approve: Document Level Task Verdict: Approved	PPD Content Approval 03-Oct-2024 10:05:35 GMT+0000

Approve: Document Level Task Verdict: Approved	PPD Content Approval 03-Oct-2024 10:34:51 GMT+0000

Approve: Document Level Task Verdict: Approved	PPD Content Approval 04-Oct-2024 14:41:05 GMT+0000

Signature Page for VV-RIM-02714615 System v3.0
D8151C00001 Statistical Analysis Plan Edition 3