Cover page

Protocol number: D8151C00001

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

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Date of the document: 03 May 2024

Clinical Study Protocol	
Study Intervention	AZD0171
Study Code	D8151C00001
Version	5.0
Date	03 May 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

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden.

Regulatory Agency Identifier Number(s)

IND number: 135273

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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D8151C00001

Amendment Number: 4
Study Intervention: Investigational AZD0171, durvalumab and standard of care gemcitabine, nab-paclitaxel

Study Phase: II

Short Title: Safety, Pharmacokinetics and Clinical Activity of AZD0171 in Combination with

Durvalumab and Chemotherapy in Locally Advanced or Metastatic Solid Tumours

Study Physician Name and Contact Information will be provided separately

International co-ordinating investigator

PPD

VERSION HISTORY

Version 5.0, [03 May 2024]

The protocol was amended to include more recent clinical results from prior studies. The following sections were updated:

- Section 2.2.3: This section was amended to include more recent safety data on AZD0171.
- Section 2.2.4: This section was amended to include more recent study data on durvalumab.
- Section 2.3.1: The risk assessment was updated to include new identified risks of durvalumab (uveitis, immune-mediated arthritis, Guillain-Barre syndrome).
- Section 4.3: This section was added to the protocol to include details of the continued treatment period.
- Section 8.2.6 (Table 13): Clinical chemistry was updated to include carbon dioxide as an alternative to bicarbonate.
- Section 9.2: The number of participants planned to be screened for this study was increased from 240 to 370.
- Section 10, Appendix A1: The regulatory reporting requirements for SAEs were updated to cover the European Union safety reporting requirements.
- Global: Minor editorial corrections (typos, formatting, abbreviations etc.) were made for document quality.

Version 4.0, [3 Mar 2023]

This amendment includes clarifications identified from previous feedback on the clinical study protocol have been included, as follows:

- Sections 1.3 (Table 2) and 8.2.3 Table 11: Section amended to add pre-dose ECG measurement at Cycle 1 Day 1, Cycle 2 Day 15, and Cycle 4 Day 1 to enable collection of high quality ECG data.
- Section 2.2.3: Addition of safety information from the first 41 patients enrolled in this study.
- Section 2.3.2: Section amended to fix spelling of periodic to periodontal.
- Sections 4.1 and 6.2.6: Section amended to clarify that the patient monitoring for at least 30 minutes after the end of last infusion Day 1 of each cycle is required, but this is not necessary on Day 8 and Day 15.
- Section 5.2: Introduced clarifications in wording for Exclusion 4 on thromboembolic events.

• Section 5.4: Added context to better explain instances where rescreening of patients would be allowed. • Section 6.2.5: Removed the wording about patients being greater than or equal to 35 kg weight. • Section 6.6.1: Added information regarding a chemotherapy holiday. Updates to align with latest sponsor protocol template wording have been added: Sections 4.4, 8.3.11, A6, A7, A9, A11, and E4.
Version 3.0, [10 May 2022]
This amendment includes changes in response to durvalumab Investigator's Brochure update in the following sections: • Section 2.3.1 and 8.3.6.2: Updated safety information per Investigator's Brochure update for durvalumab. Language on staggered enrolment approach for safety run-in participants has been included. In addition, clarifications identified from previous feedback on the clinical study protocol have been included, as follows: • Sections 1.1, 1.3 (Table 2), 3, 4.1, 4.2.2, 8.5.1, 8.5.1.1, 8.5.3.2, 9.4.5.1, 9.4.6.1, and 9.4.6.2: Sections amended to remove total leukaemia inhibitory factor from pharmacokinetic (PK) endpoint and to add it as a pharmacodynamic endpoint. • Sections 1.1 and 2.1: Deletion of "rates" after treatment response/survival. • Sections 1.1, 3, and 4.2.2: Language on secondary efficacy endpoint updated for clarity. • Sections 1.1 and 4.1: Updated approximate number of sites participating in this study. • Sections 1.1 and 9.4.2: Deletion of "rates of" before objective response rate and disease control rate. • Sections 1.1 and 9.6: Clarification that additional safety reviews may be conducted at the discretion of the Safety Review Committee (SRC). • Section 1.3 (Table 2): Additional plasma sample for circulating tumour DNA will be taken on Cycle 1 Day 1 for accurate assessment of baseline level. Updated Table footnote for correction and clarification that anti-drug antibodies (ADA) samples are collected on pre-dose PK timepoints on specified days. • Section 4.1: Clarification that staggered approach to dosing of study intervention may be required for safety run-in participants and when ambiguous findings or unexplained safety issues occur or if deemed necessary by SRC.

- Sections 4.1 and 6.2.6: Clarification that all participants will be monitored for at least 60 minutes after the end of last study intervention infusion on Cycle 1 Day 1, and 30 minutes after the end of last infusion on subsequent visits.
- Sections 4.1.2, 5.4, 7.1.4, and Appendix B 2: Section amended to state that participants can be rescreened only once.
- Section 4.2.2: Updated to correct that overall survival is not the primary endpoint.
- Section 4.3.1.1: Section amended to align wording with interpretation and conclusions of modelling.
- Section 4.3.1.2: Section amended to include information from Phase I study.
- Section 4.3.2.1: Language on data from completed studies on durvalumab was updated for better clarity.
- Section 4.4: Definition of end of study was amended for simplification.
- Section 5.1: Clarification added to state that:
    - the window of all eligibility criteria applies within 28 days prior to Cycle 1 Day 1.
    - the participants with metastatic pancreatic adenocarcinoma are eligible.
- Section 5.2.:
    - Updated exclusion criterion 4 of patients with thromboembolism to align with the clinical practice based on patient population.
    - Updated exclusion criterion 8 as the benefit/risk of enrolling participants with positive Coronavirus disease 2019 (COVID-19) testing has changed due to changes in the COVID-19 pandemic situation. This change in eligibility criteria aims to increase trial access for patients with life-threatening pancreatic cancer once investigators have considered the overall well-being and best interests of trial participants.
    - Updated exclusion criterion 14 to clarify the exceptions to this criterion.
- Sections 6.1.1, 6.1.1.4, and 6.1.2: Updated Section number 6.1.1.4 to 6.1.2 and moved Table 6 under the new section for clarification that chemotherapy is not investigational medicinal product.
- Section 6.2.2: Clarification added to state that the window for AZD0171 standard infusion time is 60 min (+ 10 minutes).
- Section 6.2.4: Updated wording to state that “Durvalumab IV infusion will start 15 minutes after the end of AZD0171 infusion” for consistency with Section 6.2.5.
- Section 6.2.5: Figure 2 footnote for the waiting time between Day 15 AZD0171 infusion and nab-paclitaxel IV infusion was updated to “15-30 minutes”.
- Section 6.6.1: Clarification added for chemotherapy dosing and interruptions due to adverse event (AE)/toxicity in a cycle.

- Section 6.7: Section amended to clarify that participants may be limited to 2 years immunotherapy treatment.
- Section 8.2.2 (Table 9): A footnote was added in Table 9 to clarify that pre-dose and end of infusion vital signs are required for each individual chemotherapy.
- Section 8.5.1 and 8.5.1.1:
    - Section 8.5.1 text was amended to clarify that pre-dose PK samples for AZD0171 and durvalumab, matched to ADA samples, will be collected from all participants.
    - Text was amended in Section 8.5.1 and a footnote was added in Tables 18 and 19 to state that Day 8 AZD0171 pre-dose PK sample will be collected prior to the chemotherapy administration.
    - Table footnote was added in Tables 18 to 22 to state that times for collection of durvalumab PK samples are relative to durvalumab infusion.
    - A footnote was added in Table 21 to state that pre-dose durvalumab PK samples matched to ADA samples will be collected from all participants.
    - Text amended in Section 8.5.1 and Table footnote was added in Tables 23 and 24 to state that chemotherapy PK timepoint applies to each chemotherapy.
    - A footnote in Table 24 was removed as ADA samples are not collected for chemotherapy.
- Section 8.5.3.2: Clarification that serum samples for total LIF will be collected at the same time as AZD0171 PK samples.
- Section 8.5.3.4:
    - Clarification that paired screening and on-study tumour biopsy specimens with sufficient and evaluable tissue material are required from up to 20 participants
    - Clarification on provision of on-study tumour biopsy.
    - Clarification that CCI [redacted] may also be used for correlative studies.
- Section 9.1: Text that had been erroneously presented under subheadings of "Primary Hypothesis" and "Secondary Hypothesis" (previously, Sections 9.1.1 and 9.1.2) was deleted because there is no hypothesis testing being done in this study.
- Appendix A 3: Section amended to state that participants who are rescreened are required to sign a new informed consent form.
- Global: Minor editorial corrections (typos, formatting, etc.) were made for document quality.

Version 2.0, [16 July 2021]

This amendment includes changes in response to FDA queries, which are:

- Section 6.2.4: Section amended to state that a dose of 1500 mg durvalumab will be prepared for participants > 30 kg in weight.
- Section 6.2.5: Clarification added to state that for participants > 30 kg or weight-based dosing at 20 mg/kg for participants ≤ 30 kg, as applicable, durvalumab 1500 mg will be administered over 60 minutes by IV infusion, 15 minutes after the end of AZD0171 infusion.
- Section 6.5.2: Information added to state that Investigator clinical judgement should be exercised to ensure participants are eligible to receive gemcitabine and nab-paclitaxel in accordance with the guidelines in the local package insert, prior to first dose of study intervention and during the study. In addition, caution should be exercised (or alternative medication should be considered) when nab-paclitaxel is administered concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

In addition, minor clarifications identified from previous feedback on the clinical study protocol have been included, as follows:

- Section 1.3: Serum LIF samples have been added on Day -3 of Cycle 1.
- Section 5.2: Exclusion criterion 11 amended to state that mean QTcF ≥470 ms will be calculated from 3 ECGs (within 5 minutes at 1 minute apart).
- Section 6.1.1.2: Addition of 25mM histidine to the AZD0171 solution.
- Section 6.2.2: Section amended to state that a dose of CCI mg AZD0171 will be prepared for participants ≥ 35 kg in weight.
- Section 6.2.4: Section amended to state that a dose of 1500 mg durvalumab will be prepared for participants > 30 kg in weight.
- Section 6.2.5: Clarification added to state participants will be ≥ 35 kg for AZD0171 CCI mg.
- Section 6.2.5: Clarification added to state that for participants > 30 kg or weight-based dosing at 20 mg/kg for participants ≤ 30 kg, as applicable, durvalumab 1500 mg will be administered over 60 minutes by IV infusion, 15 minutes after the end of AZD0171 infusion.
- Section 6.5.2: Information added to state that Investigator clinical judgement should be exercised to ensure participants are eligible to receive gemcitabine and nab-paclitaxel in accordance with the guidelines in the local package insert, prior to first dose of study intervention and during the study. In addition, caution should be exercised (or alternative medication should be considered) when nab-paclitaxel is administered concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

• Section 9.4.3.1: Section amended to state that treatment-emergent adverse events will be recorded on or after first dose of study intervention and within 90 days after last dose of study intervention or up to the day prior to start of subsequent therapy, whichever comes first, as well as worsening of pre-existing events, which will also be recorded on or after first dose of study intervention and within 90 days after last dose of study intervention or up to the day prior to start of subsequent therapy, whichever comes first.

Version 1.0, [17 May 2021]
INITIAL CREATION

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol 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

Short Title: Safety, Pharmacokinetics and Clinical Activity of AZD0171 in Combination with Durvalumab and Chemotherapy in Locally Advanced or Metastatic Solid Tumours

Rationale: Leukaemia inhibitory factor (LIF) is an immunosuppressive cytokine linked to tumourigenesis/metastasis. Elevated levels of LIF expression correlate with poor clinical outcomes and chemoresistance. In tumour biopsy samples and blood from pancreatic ductal adenocarcinoma (PDAC) patients, LIF levels are elevated and significantly correlate with disease pathology worsening (tumour cell differentiation), high levels of the PDAC CCI carbohydrate antigen 19–9 (CA19–9), and poor treatment response/survival. In pre-clinical tumour models of pancreatic cancer, LIF promotes tumour-initiating cell biology and epithelial-mesenchymal transition, and the combination of anti-LIF with gemcitabine improves survival. Furthermore, LIF also promotes an immunosuppressive tumour microenvironment, reducing recruitment of cytotoxic cluster of differentiation 8 (CD8+) effector T cells to tumours. In pre-clinical tumour models anti-LIF sensitises tumours to blockade of PD1 / PD-L1 immune checkpoint to induce tumour regression and antitumour immunity.

The effect on CD8+ T cells is significant because the presence and cross-linking of programmed cell death proteins between T cells and tumour cells is a mechanism that limits tumour infiltrating CD8+ T cell effector function through immune checkpoint signalling. Interestingly, combined effects of anti-LIF and immune checkpoint inhibition further induce tumour regression and improve survival in pre-clinical tumour models. Taken together, anti-LIF has the potential to aid standard-of-care chemotherapy to overcome chemoresistance and work additively or synergistically alongside anti-PD-L1 durvalumab to achieve a robust antitumour response in PDAC.

The proposed study is designed for PDAC patients to receive standard-of-care chemotherapy in combination with AZD0171 (anti-LIF) and durvalumab (anti-PD-L1).

Additional cohorts for different tumour types may be explored and added in a future amendment to the clinical study protocol (CSP).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess safety and tolerability of AZD0171 in combination with durvalumab and chemotherapy in participants with first line (1L) metastatic PDAC (mPDAC)	• Incidence of adverse events (AEs), immune mediated AEs (imAEs) and serious AEs (SAEs) • Clinically meaningful changes from baseline in clinical laboratory parameters, vital signs, and ECG results
• To determine the preliminary OS of AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC	• Overall survival at 12 months (OS-12)
Secondary	
• To further characterise the preliminary (i) antitumour activity of and (ii) survival activity after treatment with AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC	• (i) According to RECIST v1.1: – Objective response rate (ORR), disease control rate (DCR), duration of response (DoR) • (ii) Median progression free survival (PFS), PFS at 4 months (PFS-4), median overall survival (OS)
• To assess the preliminary antitumour activity of AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC via circulating CCI	• Serum CA19-9
• To assess immunogenicity of AZD0171 and/or durvalumab	• Incidence of detectable anti-drug antibodies (ADAs) against AZD0171 and/or durvalumab in serum
• To determine the pharmacokinetic (PK) profile of AZD0171, durvalumab, and chemotherapy (gemcitabine and nab-paclitaxel) in participants with 1L mPDAC	• Summary of PK parameters for AZD0171, durvalumab and chemotherapies and/or their metabolites (ie, C_{max}, AUC, CL, and terminal elimination $t_{1/2}$)
• To assess changes in CD8+ T cell tumour infiltration associated with AZD0171 treatment in combination with durvalumab and chemotherapy in participants with 1L mPDAC	• Assessment of CD8+ T cell tumour infiltration in tumour samples at baseline and on-treatment
• To assess absolute values and the change from baseline in LIF bound to AZD0171 (total LIF)	• Assessment of total LIF concentration at baseline and on-treatment

For exploratory objectives and endpoints, see Section 3 of the CSP.

Overall Design

This is a Phase II, open-label, single arm, multicentre study to assess the safety, preliminary antitumour activity, immunogenicity, PD, and PK of AZD0171 in combination with durvalumab and chemotherapy (gemcitabine and nab-paclitaxel) in participants with 1L mPDAC.

Number of Participants: Approximately 115 participants with 1L mPDAC will be enrolled at up to approximately 40 to 50 sites globally

Intervention Groups and Duration: Participants will receive in each 28-day cycle, AZD0171 (CCI mg intravenous [IV]every 2 weeks [Q2W]) along with durvalumab (1500 mg IV every 4 weeks [Q4W]) and chemotherapy IV (gemcitabine 1000 mg/m^2 + nab-paclitaxel 125 mg/m^2 on Days 1, 8 and 15 in each cycle). All participants will be treated until progressive disease or unacceptable toxicity or withdrawal of consent or another discontinuation criterion is met. All participants will be followed for survival until the end of study.

No dose reductions of AZD0171 and durvalumab will be allowed. Dose modification and toxicity management for AZD0171 and durvalumab -related toxicity, including management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions will be provided in the Toxicity Management Guidelines (provided as an Annex to the CSP).

Data Monitoring Committee: No

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. Additional safety reviews may be conducted at the discretion of the SRC.

Statistical Methods

Tabular summaries will be presented as defined in the SAP. Categorical data will be summarised by the number and percentage of participants in each category. Continuous variables will be summarised by descriptive statistics.

Efficacy: For the primary efficacy endpoint the Kaplan-Meier method will be used to estimate the OS probability and the proportion of participants surviving at 12 months, OS-12, with 80% CI. The secondary endpoints, ORR and DCR based on RECIST v1.1 will be summarised with 80% CI estimated using the exact binomial distribution. Time-to-event endpoints (DoR, PFS, PFS-4, and OS) will be analysed using the Kaplan-Meier method.

Safety: Safety data including AEs, SAEs, laboratory evaluations and vital signs results will be

summarised for all participants based on the safety analysis set. Summary statistics will be provided for AEs, imAEs, including AESIs, SAEs, and AE grade (severity) and relationship to study interventions (AZD0171, durvalumab, and chemotherapy), clinical laboratory parameters, ECGs, and vital signs. AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 and described by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities with toxicity grades according to the NCI CTCAE v 5.0 will be derived and summarised.

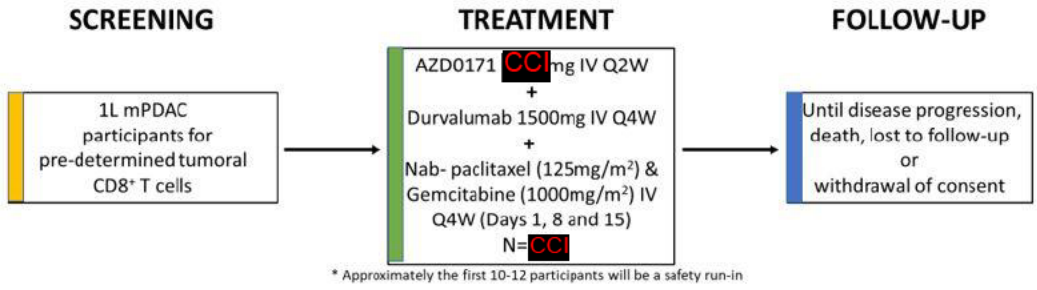
Immunogenicity: The immunogenic potential of AZD0171 and durvalumab will be assessed by summarising the number and percentage of participants who develop detectable ADAs.

Pharmacokinetics: Pharmacokinetic analyses will be performed using the PK analysis set. Plasma concentrations for individual AZD0171, durvalumab and chemotherapies and/or their metabolites will be tabulated along with descriptive statistics. Non-compartmental PK data analysis will be performed from each study intervention with scheduled PK sample collection where data allow.

Pharmacodynamics: Descriptive statistics will be used for participant and treatment specific changes from baseline in CD8+ T cell tumour infiltration. Serum CA19-9 and total LIF may be similarly analysed.

1.2 Schema

Figure 1 Study Design



Abbreviations: CD8+=cluster of differentiation 8; PDAC=pancreatic ductal adenocarcinoma; Q2W=every 2 weeks; Q4W=every 4 weeks; 1L=first line treatment; IV=intravenous.

1.3 Schedule of Activities

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time.

Table 1 Schedule of Activities (Screening)

Procedure	Screening (Day -28 to Day -1)	Details in CSP Section or Appendix
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

Procedure	Screening (Day -28 to Day -1)	Details in CSP Section or Appendix
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 . If CCI is not available within 3 months of signed informed consent or if the CCI 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). 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 2 Schedule of Activities (Treatment Period)

Procedure	Treatment Period/Cycle Day																		Details in CSP Section or Appendix
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
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	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
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 for 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
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.

[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 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] AZD0171 ADA samples collected on Day 1 and 15 of Cycles 1 and 2, and Day 1 of indicated subsequent cycles, should be collected at the same time as the pre-dose PK samples. Durvalumab ADA samples should be collected at the same time as Day 1 pre-dose PK samples of each indicated cycle.

[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 PK (Cycle 1 and Cycle 4 Day 1) and chemotherapy (gemcitabine and nab-paclitaxel) PK (Cycle 1 and Cycle 4 Day 15). Only pre-dose PK samples for AZD0171 and durvalumab, matched to ADA samples, will be collected in participants 41 to 115. 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.

[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 3 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**
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

Procedure	EOT/ Cycle Day	Follow-up (FUP) Post EOT/ Cycle Day			Details in CSP Section or Appendix
	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	
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
[redacted] 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.

2 INTRODUCTION

This is a Phase II, open-label, single arm, multicentre study of AZD0171 in combination with durvalumab (IMFINZI®) as an addition to standard of care chemotherapy (gemcitabine and nab-paclitaxel) in participants with 1L mPDAC. The term "study intervention" throughout the CSP, refers to study treatment/drug (AZD0171, durvalumab, or standard of care chemotherapy). The term "Investigational product" where used refers to AZD0171 and/or durvalumab.

2.1 Study Rationale

Leukaemia inhibitory factor is an immunosuppressive cytokine linked to tumourigenesis/metastasis. Elevated levels of LIF expression correlate with poor clinical outcomes and chemoresistance. In tumour biopsy samples and blood from PDAC patients, LIF levels are elevated and significantly correlate with disease pathology worsening (tumour cell differentiation), high levels of the PDAC CCI CA19–9, and poor treatment response/survival (Shi et al, 2019). In pre-clinical tumour models of pancreatic cancer, LIF promotes tumour-initiating cell biology and epithelial-mesenchymal transition, and the combination of anti-LIF with gemcitabine improves survival (Shi et al, 2019, Wang et al, 2019). Furthermore, LIF also promotes an immunosuppressive tumour microenvironment, reducing recruitment of cytotoxic CD8+ effector T cells to tumours. In pre-clinical tumour models anti-LIF sensitises tumours to blockade of PD1 / PD-L1 immune checkpoint to induce tumour regression and antitumour immunity (Pascual-García et al, 2019).

The effect on CD8+ T cells is significant because the presence and cross-linking of programmed cell death proteins between T cells and tumour cells is a mechanism that limits tumour infiltrating CD8+ T cell effector function through immune checkpoint signalling. Interestingly, combined effects of anti-LIF and immune checkpoint inhibition further induce tumour regression and improve survival in pre-clinical tumour models. Taken together, anti-LIF has the potential to aid standard-of-care chemotherapy to overcome chemoresistance and work additively or synergistically alongside anti-PD-L1 durvalumab to achieve a robust antitumour response in PDAC.

The proposed study is designed for PDAC patients to receive standard-of-care chemotherapy in combination with AZD0171 (anti-LIF) and durvalumab (anti-PD-L1).

Additional cohorts for different tumour types may be explored and added in a future amendment to the CSP.

2.2 Background

2.2.1 Disease Background

Pancreatic Ductal Adenocarcinoma accounts for 2.6% of global cancer cases and is the third and fourth most common cause of cancer death in the US and Europe, respectively (GLOBOCAN, 2020). In 2012, approximately 337,972 new cases of pancreatic cancer were recorded globally with 330,391 reported deaths (GLOBOCAN, 2012). By 2020, this had increased (47%) to 495,773 with an estimated increase (41%) in reported deaths to 466,003 (GLOBOCAN, 2020). Projections estimate that PDAC will become the second leading cause of cancer-related death in the US by 2030 (Rahib et al, 2014). Currently, PDAC accounts for 90% of pancreatic cancers and has an extremely poor prognosis (Kleeff et al, 2016). The aggressiveness of the disease is reflective in the 1-year survival rate of less than 25% for PDAC (Latenstein et al, 2020 and National Cancer Institute, 2018) and an estimated 5-year survival rate of less than 8% (Siegel et al, 2020).

The abundance of cytotoxic T cell infiltrates has important implications for patient outcome and therapeutic design for PDAC. A high number of CD8+ lymphocytes were significantly and independently associated with longer overall survival (Fukunaga et al, 2004, Zhang et al, 2017, Orhan et al, 2020, Liu et al, 2021). Higher levels of baseline CD8+ T cells were also associated with improvements in PFS with PDAC patients treated with nab-paclitaxel, gemcitabine and anti-PD-1 (Wainberg et al, 2020). The levels of CD8+ T cells in these patients are considered low in both primary and basal metastatic tumour tissues. The rationale for selection of participants with baseline CD8+ T cells is that they will maximally benefit from immune checkpoint inhibition.

Based on a pre-determined benchmarked PDAC external sample set, a 25% quartile cut-off will likely include 75% of pancreatic cancer patients which may predict response to immunotherapy-based treatment along with standard of care chemotherapy. In the proposed study, CD8+ T cells in pancreatic tumour tissue will be assessed by a central laboratory using an histological method to determine study eligibility for the proposed single arm trial assessing the role of AZD0171 and durvalumab as addition to standard of care nab-paclitaxel and gemcitabine-based chemotherapy. This approach may be able to find a subset of PDAC patients who will benefit from these additional immunotherapy agents to standard of care chemotherapy.

2.2.2 Chemotherapy Treatment in Pancreatic Ductal Adenocarcinoma

Current treatment guidelines in PDAC are based on diseases stage presentation at diagnosis (American Joint Committee on Cancer 2017). The majority of patients (80-90%) present with late stage clinical disease with locally advanced, distant metastases or borderline-resectable/non-resectable tumours. Systemic disease is treated with chemotherapy combinations that constitute the first line treatment.

NCCN guidelines (NCCN v2.2021), recommend the use of gemcitabine and nab-paclitaxel as category 1 for patients with ECOG performance status 0 to 2, whereas FOLFIRINOX is reserved for those patients with good performance status (0-1) due to a better tolerability profile of the former regimen. Importantly, NCCN recommends the use of olaparib as maintenance therapy for patients who harbor breast cancer type 1/type 2 (BRCA1/2) germline mutations and respond or have stable disease with platinum containing chemotherapy. Similarly, ESMO guidelines (Ducreux et al, 2015) recommend gemcitabine and nab-paclitaxel as first line therapy for patients with ECOG performance status 0 to 1. Overall, these chemotherapy combinations provide a median OS of less than 12 months. Therefore, PDAC still remains a fast growing disease of poor prognosis with a high unmet clinical need.

The recent approvals of immunotherapy for many types of tumours has raised interest on whether these agents would be effective in the treatment of PDAC alone or in combination with chemotherapy. Interestingly, PD-1 blockade using pembrolizumab in combination with gemcitabine and nab-paclitaxel showed improved OS of 15 months (Singh and O'Reilly, 2020). Furthermore, the combination of durvalumab + tremelimumab + gemcitabine and nab-paclitaxel showed an OS of 9.8 months and an encouraging ORR of 30% (Renouf et al, 2020). Additionally, targeting the CD40 pathway in PDAC has yielded some interesting results in a recent Phase I study. The combination of gemcitabine and nab-paclitaxel with nivolumab + anti-CD40 was shown to be tolerable with an ORR of 67% and OS of 10.3 months, although the number of patients were limited and requires further confirmation (O'Hara et al, 2021).

Despite the numerous preclinical studies that showed initial efficacy of immunotherapy combinations, no large Phase II/III studies to date have confirmed the initial findings. In this regard, one of the main challenges of immunotherapy in PDAC is the unique tumour immune microenvironment where the presence of CD8+ T cells has been associated with favourable prognosis (Knudsen et al, 2017). Therefore, selection of participants with higher frequencies of CD8+ T cells could possibly increase responses and survival rate. To this end, the opportunity to combine immunotherapy approaches that will synergise the demonstrated efficacy of chemotherapy (gemcitabine and nab-paclitaxel) might lead to increased efficacy.

2.2.3 AZD0171

AZD0171 is a first-in class-humanised mAb of the IgG1κ subclass that binds potently and specifically to LIF - an immunosuppressive human cytokine. Leukaemia inhibitory factor is a member of the IL6 family of cytokines (Nicola and Babon, 2015) and AZD0171 inhibits LIF signalling by blocking recruitment of the gp130 receptor subunit to the LIF receptor subunit. As a result, this prevents downstream receptor signalling and phosphorylation of STAT3. In a Phase I study (MSC-1-101), AZD0171 monotherapy in advanced solid tumours showed a favourable safety profile at all doses with no dose-limiting toxicities. Thirteen patients (34.2%) had a best overall response of SD and the remaining patients had progressive disease. A prolonged SD > 16 weeks was observed in 23.7% of patients on the study. Overall median

PFS was approximately 6 weeks (min, max of 2 to 28 weeks).

CCI

[redacted]

Further details of the non-clinical and clinical experience with AZD0171 are provided in the current AZD0171 IB.

2.2.4 Durvalumab

Durvalumab is a human mAb of the IgG1κ subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of cancer. The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition

of immune responses, including those that may result in tumour elimination. In vitro studies demonstrate that durvalumab antagonises the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al, 2015). In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T cell dependent mechanism (Stewart et al, 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumour immune response by binding to PD-L1 and shifting the balance toward an antitumour response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

As of the DCO date of 30 April 2023, an estimated 16852 patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumour types, stages of disease and lines of therapy. The safety profile of durvalumab as monotherapy and combined with other anticancer agents is consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. Most ADRs seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues and could occur in any organ system. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment and, in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity.

Further details of the non-clinical and clinical experience with durvalumab is provided in the current durvalumab IB.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Potential Risks

CCI [redacted].

Identified risks with durvalumab include diarrhoea/colitis, pneumonitis and ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus, and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis including

pemphigoid, myocarditis, myositis/polymyositis, pancreatitis, encephalitis, IRRs, myasthenia gravis, uveitis, immune-mediated arthritis, Guillain-Barre syndrome, and immune thrombocytopenia. Potential risks with durvalumab include hypersensitivity reactions, including anaphylaxis, infections, immunogenicity, cytokine release syndrome, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barre syndrome). For information on all identified and potential risks with durvalumab, refer to the current durvalumab IB.

CD8+ assessment for eligibility will be performed using tissue obtained as part of standard of care diagnostic biopsy. If diagnostic biopsy sample is not available, investigator may perform CCI based on risk assessment and only if considered safe to perform.

Potential Combination Toxicity

CCI [redacted]

The design of the current study aims to minimise potential risks to participants based on the CSP inclusion and exclusion criteria, restrictions on concomitant medication during the study, safety monitoring (including review of all safety, PK, and other relevant data by the safety review committee), and TMGs. The potential risks associated with the toxicity of the combination regimen are designated AESIs and hence are subject to intensive safety monitoring.

2.3.2 Benefit Assessment

Metastatic PDAC is a disease with an extremely poor prognosis, for which standard-of-care chemotherapy has limited impact on survival. As such, there is a significant unmet medical need for this patient population which require novel therapies.

AZD0171 is considered to have a favourable safety profile for participants with mPDAC. Pre-clinical data suggest that a robust antitumour response in patients with PDAC may be achieved with anti-LIF activity in combination with anti-PD-L1 therapy.

In a mouse PDAC model, LIF-neutralising antibodies plus gemcitabine induced a robust antitumour response by reversing suppression of effector T cells (Wang et al, 2019). Similarly, anti-LIF in combination with anti-PD-1 demonstrated antitumour activity and improved survival (Pascual-García et al, 2019). This indicates the therapeutic potential of AZD0171 to enhance the antitumour response when used in combination with standard-of-care

chemotherapy and immune checkpoint inhibition in mPDAC.

Importantly, CD8+ cytotoxic T cells play a significant role in the observed antitumour activity in murine tumour cancer models and they are important for antitumour responses in a number of human solid tumour malignancies including PDAC (Balachandran et al, 2017).

Early proof of concept data from a Phase I dose finding study (MSC-1-101) in 41 patients showed 34.2% of patients as having SD. A total of 23.7% of patients had SD ≥ 16 weeks; 1 patient had SD for 28 weeks. AZD0171-related AEs, as assessed by the investigator, were reported in 46.3% of patients, the majority being Grade 1, and the most common being fatigue (19.5%) and nausea (9.8%). Grade 1 AZD0171-related AEs (increased AST, increased ALT), Grade 2 AZD0171-related AE (GGT increase) and Grade 3 AZD0171-related AE (increased AST) were reported. There were no reports of Grade 4 or 5 AZD0171-related events were reported. There was 1 case of AZD0171-related SAE reported, Grade 2 osteonecrosis of the mandible, in a head and neck cancer patient who had previously received high dose radiation to the area and had a history of receptor activator of nuclear factor kappa-B ligand (RANKL) -inhibitor therapy (denosumab) and active periodontal disease. There were no DLTs or discontinuations due to AZD0171-related AEs.

Notably, AZD0171 monotherapy increased the frequency of CD8+ T cells in matched on-treatment vs pre-treatment biopsies in a subset of participants. The potential for AZD0171 to reinvigorate T cell response or tumour infiltrating lymphocytes may be of clinical benefit in participants with basal detectable tumoral CD8+ T cells especially when combined with an immune checkpoint inhibitor.

Additionally, the emerging safety data described in section 2.2.3 from this Phase 2 study are consistent with recent findings from other 1L mPDAC studies (Padrón et al, 2022, Tempero et al, 2021).

Therefore, targeting LIF with AZD0171 in combination with durvalumab and standard-of-care chemotherapy may lead to more synergistic durable responses in 1L mPDAC participants with pre-determined tumoural CD8+ T cells.

Participants in this study will benefit from the monitoring of all AEs arising during the clinical study, related or not related to the study intervention. In addition, they will be contributing to the development of new therapies for advanced cancer.

2.3.3 Overall Benefit: Risk Conclusion

All study participants will receive nab-paclitaxel plus gemcitabine which is a current globally accepted standard of care for PDAC which will give benefits similar to other PDAC patients for their disease. Taking into account the measures taken to minimise risk to participants enrolling in this study, the potential risks identified in association with AZD0171 and

durvalumab when added to standard-of-care chemotherapy, are justified by the anticipated benefits that may be afforded to participants with mPDAC.

Further details can be found in the current AZD0171 and durvalumab IBs.

2.3.4 Benefit/Risk Pertaining to Study Conduct During the COVID-19 Pandemic

Cancer patients have an increased risk of exposure to SARS-CoV-2 due to frequent hospital or clinic visits for treatment and monitoring. A retrospective cohort study of 28 COVID-19-infected cancer patients from 3 hospitals in Wuhan, China, reported that a third of patients (28.6%; N = 8) were suspected to have acquired the infection by hospital-associated transmission (Yu et al, 2020, Zhang et al, 2020). Patients with cancer may have a higher risk from COVID-19 than individuals without cancer but current evidence appears insufficient to support a conclusive association between cancer in general and COVID-19 (Kumar et al, 2019, Xia et al, 2020).

This study will enrol participants with PDAC. Participants in this study will receive antibody interventions that lead to inhibition of LIF and PD-L1 as part of the treatment strategy. Overall, the interventions received and procedures during the course of this study are considered to have low risk for increasing susceptibility to COVID-19 infection.

Furthermore, at this stage of disease, participants would typically have frequent healthcare-related visits, irrespective of the participation in a clinical study. Therefore, it is anticipated that overall their participation in this clinical study should not significantly increase their risk of exposure to COVID-19 infection.

Novel treatment options are needed to improve the long-term prognosis for patients with PDAC which is associated with chemoresistance, extremely poor prognosis, and a high risk of developing cancer-related death. AZD0171 could be a potential treatment option in the PDAC patient population with high unmet medical need. The scheduled safety monitoring visits that are considered in excess of standard-of-care monitoring are intended to protect participants involved in the study. Thus, although there may be increased risk to patients by exposure to SARS-CoV-2 during study visits, this is offset by the benefit that patients may receive in the form of an extended period of PFS.

In accordance with EMA and FDA guidelines (EMA-CTFG-EC 2020, FDA 2020), a risk assessment will be conducted in collaboration with investigators for each site and participant prior to site initiation/participant enrolment and on an ongoing basis throughout the study to assess whether additional measures may be necessary to ensure participant safety and data validity. Measures may include postponement of study start on a global, country, or site level or suspension of recruitment of participants in locations with an increased risk of COVID-19-related disruption.

If there is a need to reconsent study participants for the implementation of new urgent changes in study conduct, additional guidance on alternative means of obtaining reconsent to avoid unnecessary study visits is provided as Appendix A (as a supplement to the standard consent procedures in Appendix A 3 of the CSP). Any deviations to the CSP necessary to safeguard participant safety or data validity as a result of COVID-19-related disruption will be recorded and any permanent changes requiring an amendment to the CSP will be communicated to Regulatory Authorities and IRBs/IECs in line with relevant local guidance and procedures.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Type	Objectives	Endpoints
	Primary	
Safety	• To assess safety and tolerability of AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC	• Incidence of AEs, imAEs and SAEs • Clinically meaningful changes from baseline in clinical laboratory parameters, vital signs, and ECG results
Efficacy	• To determine the preliminary OS of AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC	• OS-12
	Secondary	
Efficacy	• To further characterise the preliminary (i) antitumour activity of and (ii) survival activity after treatment with AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC	• According to RECIST v1.1: – (i) ORR, DCR, DoR – (ii) PFS, PFS-4, OS
Efficacy	• To assess the preliminary antitumour activity of AZD0171 in combination with durvalumab and chemotherapy in participants with 1L mPDAC via circulating biomarkers	• Serum CA19-9
Immunogenicity	• To assess immunogenicity of AZD0171 and/or durvalumab	• Incidence of detectable ADAs against AZD0171 and/or durvalumab in serum
Pharmacokinetic	• To determine the PK profile of AZD0171, durvalumab, and chemotherapy (gemcitabine and nab-paclitaxel) in participants with 1L mPDAC	• Summary of PK parameters for AZD0171, durvalumab and chemotherapies and/or their metabolites (ie, C_{max}, AUC, CL, and terminal elimination $t_{1/2}$)
Pharmacodynamic	• To assess changes in CD8+ T cell tumour infiltration associated with AZD0171 treatment in combination with durvalumab and chemotherapy in participants with 1L mPDAC	• Assessment of CD8+ T cell tumour infiltration in tumour samples at baseline and on-treatment

Type	Objectives	Endpoints
Pharmacodynamic	• To assess absolute values and the change from baseline in LIF bound to AZD0171 (total LIF)	• Assessment of total LIF concentration at baseline and on-treatment
	Exploratory	
CCI	• CCI – CCI – CCI	• CCI • CCI • CCI – CCI
CCI	• CCI	• CCI
CCI	• CCI	• CCI – CCI – CCI
CCI	• CCI	• CCI
CCI	• CCI	• CCI

Type	Objectives	Endpoints
	CCI	CCI – CCI – CCI – CCI – CCI – CCI – CCI

Abbreviation: 1L=first line; ADA=anti-drug antibody; AE=adverse event; AUC=area under the concentration-time curve; CA19-9=carbohydrate antigen 19-9; CD=cluster of differentiation; CD8+=cluster of differentiation 8; CL=clearance; Cmax=maximum observed concentration; CCI DCR=disease control rate; DNA=deoxyribonucleic acid; DoR=duration of response; ECG=electrocardiogram; CCI imAE=immune mediated adverse events; LIF=leukaemia inhibitory factor; mRNA=messenger ribonucleic acid; ORR=objective response rate; OS=median overall survival; OS-12=overall survival at 12 months; mPDAC=metastatic pancreatic ductal adenocarcinoma; PD=pharmacodynamic(s); PD-1=programmed cell death protein 1; CCI PFS=median progression free survival; PFS-4=progression free survival at 4 months; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumours; RNA=ribonucleic acid; SAE=serious adverse event; t1/2=half-life; CCI

4 STUDY DESIGN

4.1 Overall Design

This is a Phase II, open-label, single arm, multicentre study to assess the safety, preliminary antitumour activity, immunogenicity, PD, and PK of AZD0171 in combination with durvalumab and standard of care chemotherapy (gemcitabine and nab-paclitaxel) in participants with 1L mPDAC.

Approximately 115 participants with 1L mPDAC will be enrolled at up to approximately 40 to 50 sites globally. Participants will receive in each 28-day cycle, AZD0171 (CCI mg IV Q2W) along with durvalumab (1500 mg IV Q4W) and chemotherapy IV (gemcitabine 1000 mg/m^2 + nab-paclitaxel 125 mg/m^2 on Days 1, 8 and 15 in each cycle). All participants will be treated until progressive disease or unacceptable toxicity or withdrawal of consent or another discontinuation criterion is met. The study schema is presented in Figure 1.

There will be a safety run-in setup for initial participants. The first 5 participants on the study will have at least 24 hours between each participant's dosing to ensure adequate monitoring for IRRs. All participants enrolled on the study will be monitored for at least 60 minutes after the end of last study intervention infusion on C1D1. At subsequent visits, participants will continue to be monitored for at least 30 minutes after the end of last infusion on study intervention on Day 1 of each cycle, but this is not necessary on Day 8 and Day 15. An SRC will review the safety profile after up to approximately 10 to 12 initial participants have completed the first cycle of treatment. Intensive PK of AZD0171, chemotherapy, and QT prolongation risk will also be assessed in the 10 to12 safety run-in participants.

For the safety run-in participants, a delay of approximately 7 days may be mandated between each subsequent participant prior to administration of first dose of study intervention. Providing there are no safety concerns after review by the SRC, this staggered approach to dosing of study intervention may not be required. However, should ambiguous findings or unexplained safety issues occur, the SRC may choose to stagger dosing between participants until adequate safety information is available to support exposure of a large number of study participants.

An interim analysis of ORR will be performed when approximately 40 evaluable participants have been dosed and have had opportunity to complete 2 post-baseline scans (see Section 9.5).

4.1.1 Safety Review Committee

An 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 AEs, concomitant medications or therapies, clinical laboratory

tests, vital signs, physical examinations, ECGs, and echocardiography or MUGA scans (as clinically indicated), including the incidence of dose interruptions, dose modifications, and discontinuations will be reviewed. The SRC may request additional data as needed. Additional safety reviews may be conducted at the discretion of the SRC. The SRC will reach agreement on its recommendations.

The SRC will include, but is not limited to, the following:

- SRC Chairperson (AstraZeneca Clinical Lead)
- Study Physician
- Global Safety Physician
- The PI or their delegate from each site at which participants under review were enrolled.
- Study Statistician
- SRC coordinator
- Appropriate CRO staff (for example: CRO project manager, CRO physician)

The Clinical Development Scientist, Patient Safety Scientist, and other delegates may also be invited as appropriate. Other internal and external experts may be consulted by the SRC as necessary. The membership, roles, responsibilities, and details on the process flow/communication plan will be provided in the SRC Charter.

4.1.2 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study-site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies), or local government, these changes may include the following options:

- Rescreening: Rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants; as defined in Section 5.4. Prior to rescreening, the investigator should confirm with the designated study physician.
- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the participant's next contact with the study site).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video. For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix B.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Population

This study is designed to evaluate the safety and OS-12 of AZD0171 in combination with durvalumab and chemotherapy using fixed dosing in 1L mPDAC patients.

This study will complement and add to data from the completed Phase I study (MSC-1-101). The study will assess short and long-term safety including evaluation of the nature of toxicities (AEs, SAEs, imAEs), and outcomes of treatment of events. The study will also yield in depth understanding of rare events, or new imAEs that may occur through long-term administration of study intervention.

As part of the clinical drug development programme for AZD0171, investigations into variations in PD and exploratory CCI and their relationship to drug effect are planned. These CCI may be derived from CCI There are many potential benefits of this exploratory research, including CCI This research may result in an understanding of the CCI The collection of samples is also included to allow characterisation of the PK of AZD0171 for safety.

4.2.2 Rationale for Study Endpoints

Primary Endpoints

The primary objective for the study is to determine the safety profile and tolerability including preliminary overall survival of AZD0701 and durvalumab in combination with standard-of-

care chemotherapy in 1L mPDAC. The incidence of AEs, imAEs, SAEs, and clinically significant ECGs will be used to assess the safety profile of the study intervention. The preliminary improvement in the OS-12 will be used to assess the overall survival of the study intervention. These data may allow continued development in disease-expansion cohorts and later-stage clinical trials, which will further define safety and efficacy.

Secondary Endpoints

The secondary objectives include determination of the preliminary antitumour activity of and survival activity after treatment with AZD0701 and durvalumab in combination with standard-of-care chemotherapy in 1L mPDAC according to RECIST 1.1. Specifically, ORR, DCR and DoR endpoints will be used to characterise the preliminary antitumour activity; PFS-4, median PFS and median OS will be used to assess the impact on survival. Further, preliminary antitumour efficacy will also be assessed by circulating CCI Specifically, serum levels of CA19-9 will be used to evaluate preliminary antitumour activity of the study intervention.

Additional secondary objectives include determination of PK, immunogenicity and evaluation of the PD activity of AZD0701 and durvalumab in combination with standard-of-care chemotherapy in 1L mPDAC. The PK parameters for AZD0171, durvalumab and chemotherapy and or their metabolites will be determined. Specifically, measurements of C_{max}, time to reach C_{max}, AUC, CL and $t_{1/2}$ will be used to further determine and understand PK profile of the study intervention combination. Incidence of anti-drug antibodies in serum will be used to assess the immunogenicity profile of the IMP. For PD activity, changes of total LIF concentration from baseline will be assessed. Changes in tumour infiltrated CD8+ T cells from baseline in paired tumour biopsies will be used to assess and confirm the proposed mechanism of action of the study intervention in mPDAC. Participants will only undergo new biopsies if it is considered a medically acceptable risk by the treating physician.

Exploratory Endpoints

CCI

CCI

4.3 Continued Treatment Period

The DCO for the primary endpoint will be in Q4 2024. Data analysis will be performed, and a CSR will be written based on this DCO.

Any patients still receiving IP at the time of this DCO will be able to continue to receive AZD0171 or durvalumab or both within the current study through a Continued Treatment Period. Patients are eligible for the Continued Treatment Period if the Investigator determines the patient is deriving clinical benefit from treatment and the patient has not fulfilled discontinuation criteria. If Investigators decide to keep patients on treatment, these patients may continue for 2 years.

During the Continued Treatment Period, assessments will revert to the standard of care for each individual site. Data will not be entered into the clinical study database after the DCO date. Patients will continue to be monitored for all AEs, SAEs, overdoses, and pregnancies up to 90 days after the last dose of IP. Paper-based reporting will be used for any SAE, overdose, or pregnancy identified after the DCO, and must be reported within times outlined in the protocol. All reported events will be entered into the AstraZeneca global safety database.

The Interactive Voice and Web Response System will be closed following the DCO, and sites will manually order IP. The IP dispensation and reconciliation will be handled by the study site at each participant's visit. Drug accountability information must still be collected until all participants have completed treatment.

After the DCO for the CSR, individual study sites will be closed once their final participant completes the study. The Continued Treatment Period will remain available to participants until the last participant discontinues treatment. The Last Subject Last Visit in the Continued Treatment Period is defined as the date of the last participant's final visit.

4.4 Justification for Dose

4.4.1 AZD0171

4.4.1.1 Dose Justification (AZD0171)

The selected dose and schedule of CCI mg IV Q2W of AZD0171 in this study are based on a good laboratory practice toxicology study in monkeys and the completed Phase I MSC-1-101 study.

Based on the good laboratory practice toxicology study in monkeys (10, 30 and 100 mg/kg Q1W for 4 weeks), there will be a sufficient safety margin in exposure between the cynomolgus monkey NOAEL and the selected dose and schedule of AZD0171 in this study (CCI mg IV Q2W); the estimated margins are 6.28-fold for C_{maxss} and 2.9-fold for AUC_t at steady state.

In the completed Phase I data from the MSC-1-101 study in patients with advanced solid tumours, AZD0171 was administered by one-hour IV infusion Q3W at 5 dose levels: 75 mg (2 patients), 225 mg (1 patient), 750 mg (10 patients), 1125 mg (10 patients), and 1500 mg (18 patients). AZD0171 was well tolerated in 41 treated patients including the 18 patients with the dose CCI mg Q3W. There were no DLTs or discontinuations due to AZD0171 related AEs.

A safety run-in is also incorporated in this Phase II study for the first 10 to 12 participants with CCI mg Q2W. In addition, this dose and schedule is aligned with dosing schedules for chemotherapy (gemcitabine 1000 mg/m^2 + nab-paclitaxel 125 mg/m^2 on Days 1, 8 and 15, Q4W cycle) and durvalumab (1500 mg Q4W) for clinical feasibility for mPDAC participants in this study.

Pharmacokinetic/PD/tumour receptor occupancy modelling and simulations show that CCI mg Q2W will yield a higher PK trough concentration compared to CCI mg Q3W, which potentially would result in greater target engagement. The semi-mechanistic PK/PD model predicts 80% of tumour LIF occupancy for 90% of the population for CCI mg Q2W compared to 83% of the population for CCI mg Q3W.

Overall, based on the safety margin, the completed Phase I MSC-1-101 study, clinical feasibility for mPDAC participants, PK/PD modelling, as well as the potential to drive greater downstream PD; coupled with safety lead in the current Phase II study, the selected dose and schedule of AZD0171 in this study is CCI mg IV Q2W.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD0171 is provided in the current AZD0171 IB.

4.4.1.2 Rationale for Fixed Dosing (AZD0171)

A fixed dosing approach was chosen based on preliminary population PK analysis on the Phase I clinical trial data showing no clear relationship between dose-normalised AUC or dose-normalised C_{max} with body weight in conjunction with the absence of test-article related adverse findings in animal models suggesting the potential for a wide therapeutic window in humans, and the general observation that for humanised mAbs, a fixed dosing approach appears to present an appropriate dosing scheme (Ducreux et al, 2015, Keytruda® 2020, Opdivo® 2020, Tecentriq® 2020).

4.4.2 Durvalumab

4.4.2.1 Dose Justification (Durvalumab)

The dose and schedule of durvalumab 1500 mg Q4W was selected based on PK/PD, safety and efficacy data from numerous studies containing durvalumab. As detailed in the current durvalumab IB, a fixed dose of 1500 mg Q4W (equivalent to 20 mg/kg) has been investigated

in numerous studies and found to be safe and tolerable. In completed studies conducted with durvalumab, this durvalumab dose was found to be well tolerated both in durvalumab monotherapy and in durvalumab combination therapy(ies) with other drugs. Durvalumab PK exposures observed in combination therapy were consistent with the observed monotherapy exposures.

Previous studies and PK simulations of durvalumab have indicated that a similar AUC at steady state (4 weeks) is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W. As such, durvalumab 1500 mg Q4W is considered to be equivalent to durvalumab 10 mg/kg Q2W.

Considering all available PK, safety and tolerability data, a 1500 mg Q4W dose of durvalumab is proposed in combination with AZD0171 and chemotherapy to potentially derive the maximum benefit.

4.4.2.2 Rationale for Fixed Dosing (Durvalumab)

Many published articles have previously reported a similarity of exposures following either fixed or body size-based dosing of mAbs (Ng et al, 2006, Wang et al, 2009, Zhang et al, 2012, Narwal et al, 2013). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 mAbs (Wang et al, 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/PD parameters (Zhang et al, 2012).

A fixed dosing approach is also preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, it is considered feasible to use fixed dosing regimens based on average body weight of 75 kg.

4.4.3 Chemotherapy

The standard-of-care agents gemcitabine and nab-paclitaxel being administered in combination with AZD0171 and durvalumab will be dosed according to standard practice for the regimens.

4.5 End of Study Definition

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit (FUP-2 visit) or the last scheduled procedure (survival follow-up) shown in the SoA, whichever is later.

The end of the study is defined as the date of the last visit or the last scheduled procedure for the last participant in the study, whichever comes later.

5 STUDY POPULATION

Prospective approval of CSP deviations to recruitment and enrolment criteria, also known as CSP waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Study participants will provide CCI or recently performed standard of care diagnostic biopsy for CD8+ assessment as an eligibility requirement. If diagnostic biopsy sample is not available, investigator may perform CCI based on risk assessment and only if considered safe to perform.

Participants are eligible to be included in the study only if all of the following criteria apply within 28 days prior to Cycle 1 Day 1:

Informed Consent

1) Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this CSP.
2) Written informed consent and any locally required authorisation (eg, data privacy) obtained from the participant prior to performing any CSP-related procedures, including screening evaluations.

Age

3) Participant must be aged ≥ 18 years at the time of screening or age of consent according to law.

Type of Participant and Disease Characteristics

4) ECOG performance status of 0 or 1 at screening/enrolment.
5) Life expectancy ≥ 12 weeks.
6) Must have a Gustave Roussy Immune Score (GRIm-Score) of 0 or 1
   - Neutrophil-to-lymphocyte ratio > 6 = 1 point.
   - Lactate dehydrogenase > ULN = 1 point.
   - Albumin < 3.5 g/dL = 1 point.
7) Participants diagnosed with histologically confirmed metastatic pancreatic adenocarcinoma.
8) Participants must have at least 1 measurable lesion to be called a target lesion according to RECIST v1.1.
   - A previously irradiated lesion can be considered a target lesion if the lesion is progressing and well defined.
   - For participants who undergo biopsies at screening and/or on-treatment, it is preferred though not required, that the biopsied lesion, is a target lesion.
9) All participants must consent to providing sufficient CCI taken during metastatic stage or CCI for tumoural CD8+ T cell testing for enrolment.
   - CCI sample is strongly recommended to be shipped for central testing within 2 weeks of ICF signing.
10) Presence of tumoural CD8+ T cells above a 25% quartile cut-off based on a pre-determined benchmarked PDAC external sample set by central laboratory testing.
11) Normal organ and bone marrow function measured within 28 days prior to first dose of study intervention as described below:

	Parameter	**Value**
Haematological	Haemoglobin	≥ 9.0 g/dL (5.59 mmol/L) with no blood transfusions (packed red blood cells) within 14 days prior to first dose.
	Absolute neutrophil count	≥ 1.5 × 10^9/L (1,500 per mm^3).
	Platelet count	≥ 100 x 10^9/L (100,000 per mm^3) with no platelet transfusions within 14 days prior to first dose.
Hepatic	Total bilirubin	≤ 1.5 × ULN in the absence of Gilbert's syndrome.
		≤ 3 × ULN if participant has Gilbert's syndrome.

	Parameter	Value
	Alanine transaminase and Aspartate transaminase	≤ 3 x ULN in the absence of liver metastasis. ≤ 5 x ULN in the case of liver metastasis.
	Albumin	≥ 3 g/dL.
Renal	Calculated creatinine clearance	≥ 40 mL/minute (per Cockcroft-Gault using actual body weight or 24-hour urine creatinine clearance).

Abbreviations: ULN=upper limit normal.

Weight

12) Body weight ≥ 35 kg.

Sex

13) Participants (and their sexual partners if applicable) must agree to use contraceptive(s) and should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (see Section 5.3.1).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1) Symptomatic CNS metastasis or any history of leptomeningeal disease or cord compression.
2) A participant with an already known BRCA mutation for pancreatic cancer.
3) A participant with an already known sensitising mutation or tumour characteristic for pancreatic cancer for which there is a preferred local standard of care treatment (eg, ALK, MSI etc).
4) History of thromboembolic events within the past 3 months prior to the scheduled first dose of study intervention. NOTE: Participants with venous thromboembolism without history of pulmonary embolism, who either do not require treatment or who have already been on stable treatment with anticoagulants for 14 days or longer prior to start of study intervention may be enrolled and should be closely monitored.
5) Any unresolved toxicities ≥ Grade 2 per CTCAE v5.0 from prior therapy (excluding vitiligo, alopecia, controlled diabetes).
   - Participants with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the study physician.
   - Participants with irreversible toxicity not reasonably expected to be exacerbated by treatment may be included only after consultation with the study physician.
6) History of solid organ transplantation.
7) History of active primary immunodeficiency.

8) Ongoing or an active infection, including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBsAg result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Participants with a past or resolved HBV infection are eligible. Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
   - A negative COVID-19 PCR test taken within 28 days of the start of the study treatment is required. However, fully vaccinated participants who test positive for COVID-19 can be enrolled at the investigator's discretion, provided they satisfy one of the following conditions, but should be closely monitored:
     - Remained asymptomatic for at least 5 days after the test or,
     - Had developed COVID-19 symptoms after the test but recovered, and have been asymptomatic for at least 5 days before treatment on Day 1.
9) Uncontrolled intercurrent illness, including but not limited to symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active ILD, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the participant to give written informed consent.
10) Participants with prior history of myocardial infarction, transient ischemic attack, coronary bypass, or stroke within the past 3 months prior to the first dose of study intervention.
11) Mean QTcF ≥470 ms calculated from 3 ECGs (within 5 minutes at 1 minute apart).
12) Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
   - Participants with vitiligo or alopecia.
   - Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
   - Any chronic skin condition that does not require systemic therapy.
   - Participants without active disease in the last 5 years may be included but only after consultation with the study physician.
   - Participants with celiac disease controlled by diet alone.
13) History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥ 3 years before the first dose of study intervention and of low potential risk for recurrence.
- Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease.

Prior/Concomitant Therapy

14) Receipt of any conventional or investigational anticancer therapy prior to the scheduled first dose of study intervention.
    - Participants must not have received systemic therapy for metastatic pancreatic adenocarcinoma. The exception to this criterion is if participant received prior neoadjuvant or adjuvant chemotherapy and progressed ≥ 12 months of the last dose, this participant is eligible.
15) Prior receipt of any immune-mediated therapy including, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1 antibodies, and agents targeting LIF, excluding therapeutic anticancer vaccines.
16) Use of immunosuppressive medication within 14 days prior to the first dose of study intervention is excluded. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intraarticular injection).
    - Systemic corticosteroids at physiological doses not to exceed 10 mg/day of prednisone or its equivalent.
    - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
17) Receipt of live, attenuated vaccine within 28 days prior to the first dose of study intervention (Note: Participants, if enrolled, should not receive live vaccine during the study and 180 days after the last dose of study intervention).
    - Participants can receive non-live COVID-19 vaccines, at the discretion of the investigator, following a benefit/risk evaluation for the individual participant and in accordance with local rules and regulations and vaccination guidelines. Please avoid if possible vaccine administration on same day as study intervention to clearly differentiate allergic reaction of vaccine to treatment related infusion reaction.

Prior/Concurrent Clinical Study Experience

18) Participants with known allergy or hypersensitivity reactions to any study intervention or components.
19) Concurrent enrolment in another clinical study unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

Other Exclusions

20) Documented history of alcohol or drug abuse within 6 months of signing informed consent.
21) Major surgery including highly invasive dental procedures (as defined by the investigator) within 28 days prior to scheduled first dose of study intervention or still recovering from prior surgery.
22) Females who are pregnant, lactating, or intend to become pregnant during their participation in the study or for 6 months after the last dose of study intervention.
23) Any condition that, in the opinion of the investigator, would prevent participation.
24) Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
25) Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.
26) Genetics research - future use and genomics initiative (optional):

    Exclusion criteria for participation in the optional (DNA) genetics research component of the study include:

    – Previous allogeneic bone marrow transplant.
    – Non-leukocyte-depleted whole blood transfusion in 120 days of genetic sample collection.

5.3 Lifestyle Considerations

Due to the potential risk of osteonecrosis of the jaw it is important that participants maintain good oral hygiene throughout the study and continue to see their dentist for regular check-ups during the study intervention period in addition to the oral examination by the investigator per SoA (Section 1.3)

There is no requirement for meals and dietary restrictions, caffeine, alcohol, and tobacco restrictions, or physical activity restrictions.

Restrictions for concomitant medications are described in Section 6.5.

5.3.1 Contraception

Female participants

Female participants of childbearing potential:

- Must have negative pregnancy test at screening and at Day 1 of each cycle.

- If sexually active with a non-sterilised male partner, must use at least 1 highly effective method of birth control from screening to 6 months after the last dose of study intervention.
- It is strongly recommended that sexually active non-sterilised male partners of female participants of childbearing potential use a male condom plus spermicide, from screening to 6 months after the last dose of study intervention. (Note: Male condoms are not reliable as a sole contraception method).
- Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Female participants must not breastfeed and must not donate, or retrieve for their own use, ova from screening to 6 months after the last dose of study intervention.

Male participants

Non-sterilised male participants who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening to 6 months after the last dose of study intervention.

It is strongly recommended for the female partners of a male participant to also use at least 1 highly effective method of contraception throughout this period.

In addition, male participants must refrain from fathering a child or donating sperm while on the study and for 6 months after the last dose of study intervention.

The requirements and restrictions pertaining to reproduction and contraception use for both female and male participants are further detailed in Appendix C.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals may be rescreened once. For example, those who require an urgent procedure with palliative intent (per local standard of care) to alleviate clinical symptoms leading to a delay in the initiation of treatment may be rescreened to redetermine eligibility. These rescreened participants must complete and satisfy all screening procedures within 28 days prior to Cycle

1 Day 1 – if CD8 levels are known to be positive then CD8 testing does not need to be repeated. If CD8 results are not available due to sample quality issues or logistical reasons within the initial screening time frame, participants can also be rescreened. Rescreening should occur within 28 days of initial screen failure date and participants can be rescreened a single time if benefit/risk assessment is deemed satisfactory by the investigator and confirmed by the study sponsor.

Rescreened participants should be assigned the same participant number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

These participants should have the reason for screen failure recorded in the electronic case report form (eCRF).

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), or marketed product(s), intended to be administered to a study participant according to the CSP.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Eligible participants will receive study intervention as described in Table 5.

Table 5 Investigational Products

Intervention name	AZD0171	Durvalumab (MEDI4736) [a]
Type	Biologic	Biologic
Dosage form	Concentrate for solution for infusion	Concentrate for solution for infusion
Unit dose strength(s)	20 mg/mL	50 mg/mL
Dosage level(s)	CCI mg Q2W	1500 mg Q4W
Route of administration	IV infusion	IV infusion
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	AstraZeneca R&D	AstraZeneca R&D
Packaging and labelling	Study Intervention will be provided in glass vials. Each vial will be labelled as required per country requirement	Study Intervention will be provided in vials. Each vial will be labelled as required per country requirement

[a] Label text prepared for durvalumab (MEDI4736) will show the product name as “MEDI4736” or “durvalumab (MEDI4736)” depending upon the agreed product name used in the approved study master

label document. All naming conventions are correct during this transitional period.
Abbreviations: IMP=investigational medicinal product; IV=intravenous; Q2W=every 2 weeks; Q4W=every 4 weeks.

6.1.1.1 Identity of Investigational Product(s)

The investigational product kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial is labelled with the same unique sequence number range.

6.1.1.2 AZD0171

AZD0171 will be supplied by AstraZeneca as a 200 mg vial concentrate for solution for infusion. The solution contains 20 mg/mL AZD0171, 25mM histidine, 6% (w/v) sucrose, and 0.01% (w/v) polysorbate 80; it has a pH of 6.0. The label-claim volume is 10 mL.

AZD0171 is a sterile, clear, colourless to pink solution, essentially free from visible particles.

AZD0171 Product Inspection

Each vial selected for dose preparation should be inspected. If any defects are noted with the study intervention, the investigator and site monitor should be notified immediately. Refer to the product complaint section (Section 6.1.3) for further instructions.

During the inspection if the solution is turbid or if any discoloration, or particulates are observed, the site monitor should be notified immediately and the vial(s) should be stored in QUARANTINE at refrigerated (2°C to 8°C [36°F to 46°F]) temperature for drug accountability and potential future inspection.

6.1.1.3 Durvalumab

Durvalumab will be supplied by AstraZeneca as a concentrate for solution for infusion. Durvalumab 500 mg will be supplied in a vial containing 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; the solution has a pH of 6.0 and density of 1.054 g/mL. The label-claim volume for durvalumab is 10 mL.

Durvalumab is a sterile, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

Durvalumab Product Inspection

Each vial selected for dose preparation should be inspected. If any defects are noted with the study intervention, the investigator and site monitor should be notified immediately. Refer to the product complaint section (Section 6.1.3) for further instructions.

During the inspection if the solution is turbid or if any discoloration, or particulates are

observed, the site monitor should be notified immediately and the vial(s) should be stored in QUARANTINE at refrigerated (2 °C to 8 °C [36 to 46 °F]) temperature for drug accountability and potential future inspection.

6.1.2 Gemcitabine + Nab-paclitaxel

Each standard-of-care chemotherapy agent (gemcitabine and nab-paclitaxel) will be sourced as commercially available material/locally sourced, prescribed according to local regulations, and will be administered according to prescribing information or treatment guidance in general use by the investigating site. Please refer to Tempero et al, 2017 treatment guidelines for the management of participants with mPDAC. This will be labelled with text translated into local languages in accordance with regulatory guidelines.

Eligible participants will receive chemotherapy as described in Table 6.

Table 6 Chemotherapy (Standard-of-Care)

Intervention name	Gemcitabine	Nab-paclitaxel
Type	Drug	Drug
Dose form	Solution	Solution
Dosage level(s)	1000 mg/m^2 on Days 1, 8 & 15 in each cycle	125 mg/m^2 on Days 1, 8 & 15 in each cycle
Route of administration	IV infusion	IV infusion
Use	Standard of care	Standard of care
IMP and NIMP	NIMP	NIMP
Sourcing	Provided locally by the study site, subsidiary, or designee.	Provided locally by the study site, subsidiary, or designee.
Packaging and labelling	Standard packaging and labelling	Standard packaging and labelling

Abbreviations: IMP=investigational medicinal product; IV=intravenous; NIMP=non-investigational medicinal product.

6.1.3 Reporting Product Complaints

Any defects with AZD0171 or durvalumab study intervention must be reported immediately to AstraZeneca by the site with further notification to the site monitor. All defects will be communicated to AstraZeneca and investigated further. During the investigation of the product complaint, all AZD0171 or durvalumab study intervention must be stored at labelled conditions unless otherwise instructed.

6.2 Preparation/Handling/Storage/Accountability

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines by AstraZeneca R&D supply chain. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling. Label text will be translated into local language.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the investigator instructions document.

6.2.1 Storage of AZD0171

Investigational product vials are stored at 2 °C to 8 °C (36 °F to 46 °F) and must not be frozen. Investigational product must be kept in original packaging until use to prevent prolonged light exposure.

The investigator’s or site’s designated study intervention product manager is required to maintain accurate study intervention accountability records. Upon completion of the study, copies of study intervention accountability records will be returned to sponsor. All unused study interventions will be returned to a sponsor-authorised depot or disposed of upon authorisation by sponsor according to the investigational site policy.

6.2.2 AZD0171 Infusion Preparation

The dose of AZD0171 for administration must be prepared by the investigator’s or site’s designated IP manager using aseptic technique. Total time from needle puncture of the AZD0171 vial to the start of administration must not exceed:

- 24 hours at 2 °C to 8 °C (36 °F to 46 °F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours.

No incompatibilities between AZD0171 and polyvinyl chloride and between AZD0171 and polyolefin have been observed for IV administration. A dose of CCI mg (for participants ≥ 35 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline, with a final AZD0171 concentration of 8 mg/mL and delivered through an IV administration set with a 0.2- or 0.22- µm filter. CCI . The IV bag size should be selected such that the final concentration is 8 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 60 minutes (+ 10 minutes), however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line at the same time.

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. AZD0171 does not contain preservatives, and any unused portion must be discarded.

If an IRR occurs, participants will be monitored until complete resolution of symptoms and treated as clinically indicated, including interruption and/or slowing of infusion rate as necessary (refer to TMGs Annex).

6.2.3 Storage of Durvalumab

Investigational product vials are stored at 2 °C to 8 °C (36 °F to 46 °F) and must not be frozen. The investigator, or an approved representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2 °C to 8 °C; 36 °F to 46 °F) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

Durvalumab must be kept in original packaging until use to prevent prolonged light exposure.

The dose of durvalumab for administration must be prepared by the investigator's or site's

designated study intervention manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration must not exceed:

- 24 hours at 2 °C to 8 °C (36 °F to 46 °F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours otherwise a new dose must be prepared from new vials. Durvalumab vials do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

6.2.4 Durvalumab Infusion Preparation

A dose of 1500 mg (for participants > 30 kg in weight) will be prepared using an IV bag containing 0.9% sodium chloride for injection or 5% dextrose for injection, with a final durvalumab concentration ranging from 1 to 15 mg/mL. Add 30 mL (ie, 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If participant weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be prepared using an IV bag size selected such that the final concentration is within 1 to 15 mg/mL

Durvalumab infusions are to be delivered through an IV administration set with a 0.2 or 0.22 μm filter; acceptable configurations include an IV set containing an in line filter or the attachment of a separate filter to the distal end of the IV tubing.

Durvalumab IV infusion will start 15 minutes after the end of AZD0171 infusion (see Section 6.2.5 and Figure 2). Standard infusion time for durvalumab is 60 minutes (+ 10 minutes); however, if there are interruptions, the total allowed time must not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line at the same time.

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

6.2.5 Treatment Administration

The first day of dosing is considered Day 1. Dose preparation and administration instructions

are provided in Section 6.1.1.2 for AZD0171 and in Section 6.1.1.3 for durvalumab. All study interventions will be administered on the same day. Where multiple study interventions are to be given on the same day, **the order of the administration will be: AZD0171, durvalumab, and then chemotherapy according to institutional practice** (Figure 2).

- AZD0171 CCI mg will be administered first over 60 minutes by IV infusion.
- As applicable, durvalumab 1500 mg (for participants > 30 kg or weight-based dosing at 20 mg/kg for participants ≤ 30 kg) will be administered over 60 minutes by IV infusion, 15 minutes after the end of AZD0171 infusion.

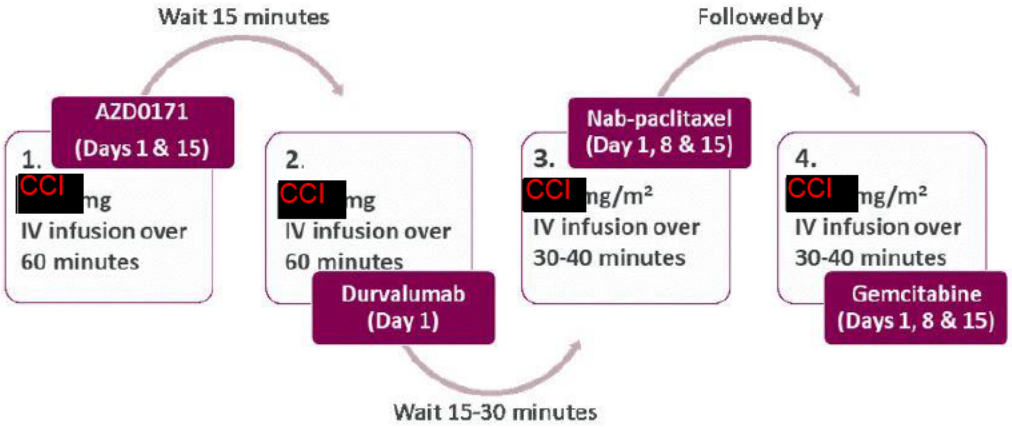
Chemotherapy agents will then be administered (as applicable, 15 to 30 minutes after the end of durvalumab infusion) according to institutional practice at the infusion times listed below:

- Nab-paclitaxel 125 mg/m^2 administered by IV infusion over 30 to 40 minutes followed by gemcitabine 1000 mg/m^2 administered by IV infusion over 30 to 40 minutes.

No specific premedication is required for AZD0171 or durvalumab. Participants should receive standard premedication according to the standard local practice for each chemotherapy. Details of any premedication or concomitant medication given to manage or prevent AEs should be recorded on the eCRF.

A physician must be present at the site or immediately available to respond to emergencies during all administrations of study intervention. Fully functional resuscitation facilities should be available. Study intervention must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.

Figure 2 Study Intervention Administration Schedule



On Day 15, wait 15-30 minutes after AZD0171 infusion before starting nab-paclitaxel IV infusion.
Abbreviations: IV=intravenous.

6.2.6 Monitoring of Dose Administration

Participants will be monitored during infusions of each study intervention, during intervals between each study intervention, and after the last infusion of study intervention. All participants enrolled in the study will be monitored for at least 60 minutes after the end of last study intervention infusion on C1D1. At subsequent visits, participants will continue to be monitored for at least 30 minutes after the end of last infusion on study intervention on Day 1 of each cycle, but this is not necessary on Day 8 and Day 15. Vital signs will be measured according to the schedules described in the SoA (Section 1.3).

Management of AZD0171 or durvalumab-related toxicities are described in Section 6.6.1. Acetaminophen and/or an antihistamine (eg, diphenhydramine) may be administered at the discretion of the investigator. If the IRR is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well. Investigators may administer steroids at their discretion as clinically indicated and per their institution's guidelines. The study physician should be informed if steroids are utilised for management of an IRR.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis.

6.3 Measures to Minimise Bias: Randomisation and Blinding

This study does not include randomisation or blinding.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study (including those administered for the treatment of AEs) must be recorded along with:

- Reason for use

- Dates of administration including start and end dates
- Dosage information including dose and frequency

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

Authorised/approved COVID-19 vaccines can be given to participants enrolled in this study as long as these do not represent a prohibited concomitant medication (see exclusion criterion 16). Investigators should follow the CSP, their local prescribing information, and policies when considering if vaccination against COVID-19 is appropriate for their participants enrolled in an AstraZeneca clinical study.

For any authorised/approved COVID-19 vaccine, specific considerations should be given to the relevant labelling information (ie, “Indications,” “Contraindications,” “Warnings and Precautions,” “Adverse Reactions”) on its use in this study including flexibility of vaccination 72 hours prior to the first dose of study intervention. In any case, COVID-19 vaccination details must be captured in the eCRF as concomitant medication, and adverse reactions reported.

6.5.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care as described in Table 7, except for those medications identified as “prohibited” as listed in Section 6.5.2.

Table 7 Permitted Concomitant Medication

Supportive Medication/Class of Drug	Usage
Premedication for management of diarrhoea, nausea, and vomiting	Permitted after but not before the first dose of study intervention
Blood transfusions	Permitted at any time after Cycle 1 Day 1
Erythropoietin	Prophylactic erythropoietin should not be started during Cycle 1 of the study but may be started during Cycle 2 and after
G-CSF	G-CSF should not be used prophylactically during Cycle 1, but may be considered after Cycle 1 following discussion with the Study Physician
Megestrol acetate	Permitted for appetite stimulation
Bisphosphonates	Permitted for treatment of bone metastases
Concomitant medications or treatments (eg, paracetamol/acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed in Table 8.	To be administered as prescribed by the investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all participants
Inactivated viruses, such as those in the influenza vaccine and COVID-19 vaccine.	Permitted

Abbreviations: G-CSF=granulocyte colony stimulating factor.

6.5.2 Prohibited Concomitant Medications

Other than the medications described above, use of concomitant medications is discouraged. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Investigator clinical judgement should be exercised to ensure participants are eligible to receive gemcitabine and nab-paclitaxel in accordance with the guidelines in the local package insert, prior to first dose of study intervention and during the study. Caution should be exercised (or alternative medication should be considered) when nab-paclitaxel is administered concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4.

Concomitant medications as described in Table 8 are prohibited (see Section 5.2).

Table 8 Prohibited Concomitant Medication

Prohibited Medication/Class of Drug	Usage
Any investigational therapy including anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the participant is on study intervention
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the participant is on study intervention. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Live attenuated vaccines	Should not be given within 28 days prior to the first dose through 180 days after the last dose of study intervention
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the immunotherapy infusions. The following are allowed exceptions: Use of immunosuppressive medications for the management of study intervention-related AEs Premedication for management of ≥ Grade 2 IRRs after Cycle 1 Day 1 per institutional standards and at the investigator's discretion; however, steroids should not be used as routine premedication for Grade 1 or 2 IRRs (refer to TMGs Annex) Use in participants with contrast allergies In addition, use of inhaled, topical, and intranasal corticosteroids is permitted A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non- immunotherapy related events experienced by the participant (eg, chronic obstructive pulmonary disease, radiation, nausea, etc)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly

Abbreviations: AE=adverse event; IRR=infusion-related reaction; TMGs=Toxicity Management Guidelines.

6.6 Dose Modification

6.6.1 Management of Study Intervention Related Toxicities

Toxicity Management Guidelines have been developed to assist investigators with the recognition and management of toxicities associated with use of AZD0171 in combination

with immune-checkpoint inhibitors, such as durvalumab (PD-L1 inhibitor). Additionally, these guidelines are applicable when AZD0171 and durvalumab are used in combination with other anti-cancer drugs (ie, antineoplastic chemotherapy, targeted agents) which are administered concurrently or sequentially as part of a CSP-specific treatment regimen.

The TMGs provide information for the management of immune-mediated reactions, IRRs, and non-immune-mediated reactions that may be observed with monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment (Section 6.6.1.3). The most current version of the TMGs, entitled “Dosing Modification and Toxicity Management Guidelines (TMGs) for AZD0171 in Combination with Durvalumab and other Products”, is provided to the investigative site as an Annex document and is maintained within the Site Master File. The TMGs detail a more conservative framework on the toxicity guidelines for immune checkpoint inhibitors and is applicable to AZD0171 in combination with durvalumab.

The following general guidance should be followed for management of toxicities. If toxicity is clearly attributed to a component of study intervention (chemotherapy or investigational product), that particular component may be discontinued or delayed (or dose reduced chemotherapy only) without any impact on other components of study intervention. For AZD0171 and durvalumab related toxicity, please follow the TMGs.

- If participants experience a toxicity clearly related to any chemotherapeutic agent necessitating the permanent discontinuation of that agent only, then the non-offending chemotherapeutic agent, durvalumab and AZD0171 may still be continued until the participant meets the guidelines for treatment discontinuation.
- In the event that durvalumab and AZD0171 is discontinued or delayed as part of the TMGs, chemotherapy may still be administered as scheduled. If AZD0171 is delayed, it will be synchronised with the durvalumab cycle.
- If chemotherapy and/or the investigational products (durvalumab and AZD0171) are withheld because of toxicity for more than 8 weeks (approximately 56 days), it is recommended the investigator contacts the study monitor if treatment planning is to be resumed.
- Study intervention cycles are scheduled as 4 weeks cycles, with chemotherapy components scheduled on Day 1, Day 8, and Day 15. If Day 1 of a new cycle cannot be dosed due to AE/toxicity, it can be dosed with delay of the cycle upon AE recovery.
- After Day 1 dosing, if a subsequent therapy visit (eg, for chemotherapy Day 8 and Day 15) cannot be dosed due to AE/toxicity, this will be considered as a dose interruption and participants should be dosed as scheduled for the next dosing visit.

- If a patient exhibits disease control after approximately 6 months of study treatment, a chemotherapy holiday (dispensing with day 8 chemotherapy) can be considered after discussion with the study physician.

If unsure how to manage a participant, the study physician should be contacted to discuss individual cases. All toxicities will be graded according to NCI CTCAE v5.0.

6.6.1.1 Management of AZD0171-Related Toxicities

The management of toxicities related to AZD0171 are also provided in the TMGs.

6.6.1.2 Management of Durvalumab-Related Toxicities

The management of toxicities related to durvalumab are also detailed in the TMGs (refer to TMGs Annex).

Participants should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other aetiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative aetiology, events should be considered potentially immune related. In addition, there are certain circumstances in which durvalumab should be permanently discontinued. Following the first dose of study intervention, subsequent administration of durvalumab can be modified based on toxicities observed as described in the TMGs.

6.6.1.3 Management of Chemotherapy-Related Toxicities

Toxicities related to chemotherapy should be managed by following local standard-of-care guidelines and prescribing information label including dose omission, dose modification, and discontinuation of therapy.

6.7 Intervention After the End of the Study

Participants are often removed from immunotherapy treatment after 2 years because the necessity for further treatment is not clear and disease control with immunotherapy can last for a year or more after the end of treatment. Therefore, participants may continue on durvalumab and AZD0171 for a total of 2 years; thereafter further discussion with the sponsor may be required for those whom the investigator considers to be benefitting from the immunotherapy treatment.

Provisions will be in place for participants still enrolled at the end of the study to continue to receive study intervention if, in the opinion of the investigator, they are continuing to receive benefit from treatment.

After the end of the study, intervention is as determined by the treating physician. Therapeutic

interventions administered during the survival follow-up period will be recorded in the eCRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive any further study intervention if any of the following occur in the participant in question:

1) Withdrawal of consent from the study or from further study intervention by participant.
2) Unacceptable toxicity/AE that in the opinion of the investigator or sponsor, warrants discontinuation of further dosing or meets criteria for discontinuation from study intervention as described here.
3) Lack of clinical activity or clinical benefit to the participant, in the opinion of the investigator.
4) Unequivocal or equivocal progressive disease. Treatment in the setting of progressive disease may continue if treatment criteria are not met (ie, absence of clinical symptoms or signs indicating clinically significant progressive disease; no decline in ECOG performance status indicating rapid decline; AND absence of rapid progressive disease or threat to vital organs/critical anatomical sites requiring urgent alternative medical intervention).
5) Initiation of alternative anticancer therapy including another investigational agent.
6) Intercurrent illness which, in the judgement of the investigator, would significantly affect assessments of clinical status.
7) Lost to follow-up.
8) Pregnancy (Section 8.3.10) or intent to become pregnant.
9) Participant is determined to have met 1 or more of the exclusion criteria for study participation at study entry and continuing treatment with study intervention might constitute a safety risk.
10) Participant non-compliance (eg, refusal to adhere to visit schedule) that, in the opinion of the investigator or sponsor, warrants withdrawal.
11) Sponsor termination of study for reasons including but not limited to unfavourable risk/benefit or change in drug development plan.

Participants who are permanently discontinued from receiving study intervention will be followed for CSP-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation (Section 7.1) or the participant is lost to follow-up (Section 7.3).

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

See the SoA for data to be collected at the time of intervention discontinuation (EOT) and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Discontinuation

Temporary discontinuations are described in Section 6.6.1.

7.1.2 Treatment Beyond Progression

Participants may continue receiving investigational products (AZD0171 and durvalumab), at the investigator's discretion, after the first overall time point assessment of progressive disease by RECIST version 1.1 until one of the following criteria is met:

- Progressive disease is confirmed on a repeat follow-up scan (unequivocal radiological progressive disease) following the initial assessment of progressive disease by RECIST version 1.1, preferably at the next tumour assessment visit and no earlier than 4 weeks after initial assessment of progressive disease.
- Participants have any significant, unacceptable, or irreversible toxicities that indicate continuing investigational products will not be of further benefit.
- Presence of clinical symptoms or signs indicating clinically significant disease progression such as the benefit-risk ratio of continuing investigational products is no longer justified.
- Decline in ECOG performance status indicating rapid decline.
- Rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumour compression, or spinal cord compression) requiring urgent alternative medical intervention (concurrent radiation treatment is not permitted), and/or continuation of investigational products that would prevent initiation of such intervention.

Participants with unequivocal or equivocal radiologic progressive disease who are eligible to continue receiving investigational products will be made aware of the potential benefits and risks of continuing investigational products in the setting of progressive disease and must provide a written informed consent prior to continuation on study intervention.

Participants who AstraZeneca and the investigator determine may not continue investigational products after progressive disease will be followed up for survival. Participants who have discontinued treatment due to toxicity or symptomatic deterioration will be followed up until radiological progressive disease and for survival. Participants who have commenced subsequent anticancer therapy will be followed up only for survival and details of subsequent

anticancer therapy/therapies collected.

7.1.3 Withdrawal of Informed Consent for Data and Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. Procedures for withdrawal from the exploratory research on collected samples are outlined in Appendix F 2.

7.1.4 Procedures for Handling Incorrectly Enrolled Participants

Participants who fail to meet the eligibility criteria (screening failures) may be rescreened as defined in Section 5.4. Participants who are enrolled (by error), but subsequently found not to meet all the eligibility criteria must not be initiated on-treatment, and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is incorrectly started on-treatment, the investigator should inform the AstraZeneca study physician or designee immediately, and a discussion should occur between the AstraZeneca study physician (or designee) and the investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca study physician or designee must ensure all decisions are appropriately documented.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an EOT visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A 9.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

  - Retesting of safety laboratory values during the screening period is allowed if clinically indicated.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the CSP-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 300 mL (over a 1-month period). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Demographics

Participant characteristics including age, gender, ethnicity (if available or allowed by local regulations), race (if available or allowed by local regulations), and geographic residence will be collected as per SoA (Section 1.3). Tobacco use, prior therapies and prior imaging (if available or allowed by local regulations) will also be collected.

Medical History

Findings from medical history collected as per SoA (Section 1.3) will be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to at or below the pre-study baseline.

Prior and Concomitant Medication and Cancer Treatment History

Prior anticancer therapy, therapy type (targeted or nontargeted) and agents received, start and end-dates, radiation therapy, and surgery received prior to study enrolment must be documented as per SoA (Section 1.3). Additionally, any medication that the participant has ingested 30 days prior to study entry, including dose, frequency and the medical condition for which it was prescribed, must be documented.

8.1 Efficacy Assessments

8.1.1 Tumour Assessments

The assessment of tumour response will be based on RECIST version 1.1 (Eisenhauer et al, 2009; see Appendix D) and will be performed according to the SoAs in Section 1.3.

All images will be collected and stored for possible future central re-analysis. It is important

to follow the tumour assessment schedule per SoA as closely as possible. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Treatment continues until clinical progression/ deterioration or confirmed radiological progression. Imaging/tumour assessments continue throughout treatment until defined radiological progression plus an additional follow-up scan (if clinically feasible) (see Section 7.1).

After discontinuation of study intervention(s), all participants will complete the EOT visit and enter follow-up; disease evaluation will be performed according to the SoA in Table 3. Additional disease assessments may be performed as clinically indicated.

Tumour assessments may include the following evaluations: cross-sectional imaging using CT or MRI scan of the chest, abdomen, pelvis; and brain. CT or MRI scan of the chest, abdomen, and pelvis will be performed with each disease assessment for all participants. Additionally, CT or MRI (preferred) scan of the brain will be performed at screening for all participants with clinical concern for brain metastasis. Any participants with brain metastases at screening or any participants who develop neurologic or other clinical symptoms that warrant imaging must also have brain imaging with each disease assessment. The preferred method of disease assessment is CT with contrast; if CT with contrast is contraindicated, CT without contrast is preferred over MRI. The preferred method for CNS imaging is MRI; if CT scan is performed, CT with contrast is required. The same method is required for all subsequent tumour assessments.

Computed tomography scan

- CT (contrast preferred) scans of the chest, abdomen, and pelvis should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. The same imaging device should be used for serial evaluations.

Magnetic resonance imaging scan

- MRI scan of the chest, abdomen, and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments.
- In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

8.1.2 Survival Assessments

The survival status of the participant will be collected as per SoA (Section 1.3) post EOT and during follow-up. After follow-up Visit 1 (28 days after last dose), participants will continue

to be followed for survival and subsequent anticancer treatment (via telephone contact with the participant or the participant's family, or by contact with the participant's current physician or email if visits are discontinued) at follow-up Visit 2 (90 days after last dose) and then Q8W from 20 weeks post last dose. The survival status (including cause of death) and the date of death or last follow-up date will be collected.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

- At screening, a complete physical examination (including body weight, height, and oral cavity) will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems (Section 1.3).
  - Study participants will have oral examination by the investigator as part of the physical examination to assess oral health status prior to first dose of study intervention. As applicable, any relevant oral health disease or symptoms considered as medical history, should be documented in the medical notes and captured in the eCRF.
- During the treatment period and follow-up period, only symptom directed physical examination (including body weight and oral cavity) is necessary.
- Physical examination information will only be reported in the eCRF if abnormalities are reported as AEs. For information on how AEs based on physical examination should be recorded and reported, see Section 8.3.5.

8.2.2 Vital Signs

- Vital signs including pulse, BP (systolic and diastolic), and temperature will be monitored at screening and at every visit during the study as per SoA (Section 1.3). Specific timing of measurement during the treatment period is described in Table 9.
- During AZD0171, durvalumab, and gemcitabine + nab-paclitaxel infusions, vital signs should be monitored as per the SoA in terms of pre-dose and post infusion measurements. Vital signs will be measured and recorded at all visits from screening to the EOT visit and follow-up visits.
- For all vital sign measurements, participants should rest for at least 10 minutes in a supine or semi-recumbent position, and all vital sign measurements should be taken prior to any blood draws or other procedures whenever possible.

Table 9 Collection Times for Vital Signs During the Study Intervention Period

AZD0171		Durvalumab		Chemotherapy [a]	
Pre-dose	**EOI**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**
Within 30 minutes	Within 15 minutes	Same as AZD0171 EOI	Within 15 minutes	Same as AZD0171 EOI or durvalumab EOI or within 30 minutes on chemotherapy only infusion days	Within 15 minutes

[a] Vital signs should be collected pre-dose and at EOI for each individual chemotherapy.
Abbreviations: EOI=end of infusion.

8.2.3 Electrocardiograms

- Resting 12-lead digital ECGs with central laboratory recording will be measured as specified in the SoA (Section 1.3). Digital recordings will be obtained after the participant has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the participant in the same physical position. Triplicate ECG recordings should be taken within a 5 minute interval (3 reads at least 1 minute apart).
- A standardised digital ECG machine should be used, and the participant should be examined using the same machine throughout the study, where feasible. During AZD0171, durvalumab, and gemcitabine + nab-paclitaxel infusions, digital ECGs should be recorded as per the SoA and collection times.
- In the safety run-in participants of approximately the first 10 to 12 participants, intensive digital ECG recordings will be obtained per Table 10. For all other participants digital ECG recordings will follow Table 11.
- In case of clinically significant ECG abnormalities including an ECG that demonstrates a QTcF value > 500 ms, 2 additional digital 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation based on the average QTcF value manually over-read by a medically qualified person. The first additional 12-lead digital ECGs should be obtained within 15 minutes.

Table 10 ECG Recording Timepoints (Safety Run-in Participants Only)

	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 4 Day 1
Safety run-in participants only	**AZD0171 Pre-dose (within 30 minutes)**		
	AZD0171 EOI ± 15 minutes		
	6 hours post AZD0171 infusion ± 30 minutes		

Abbreviations: EOI=end of infusion.

Table 11 ECG Recording Timepoints (All Other Participants)

	Cycle 1 Day 1, Cycle 2 Day 15 and Cycle 4 Day 1
All other participants	AZD0171 Pre-dose (within 30 minutes)- on C1D1, C2D15, C4D1
	End of last study intervention infusion (within 30 minutes)- on C1D1, C4D1

8.2.4 ECHO/MUGA

- Left ventricular ejection fraction will be measured by ECHO or MUGA scan at screening and as clinically indicated thereafter, eg, if the participant exhibits any symptoms indicative of myocarditis (eg, chest pain, dyspnoea, palpitations, etc) or other cardiac AEs (Section 1.3).

8.2.5 Performance Status

- Performance status will be assessed as per SoA (Section 1.3) and according to US ECOG criteria (Table 12).
- These scales and criteria are used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living abilities of the participant, and determine appropriate treatment and prognosis (Oken et al, 1982).

Table 12 Eastern Cooperative Oncology Group Performance Status

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

Abbreviations: ECOG=Eastern Cooperative Oncology Group.

8.2.6 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed at a licensed clinical laboratory at or near to the investigator site according to local standard procedures. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test).

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours). Clinically significant (as assessed by the investigator) laboratory abnormalities will be recorded in the eCRF as AEs.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The following laboratory variables listed in Table 13 (clinical chemistry), Table 14 (haematology), Table 15 (urinalysis), Table 16 (lipid panel), and Table 17 (pregnancy test) will be measured. Other safety tests to be performed at Screening include assessment for Hepatitis B surface antigen (HBsAg), hepatitis C antibodies, hepatitis A antibodies, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and human immunodeficiency virus (eg, HIV-1 and HIV-2) antibodies.

Table 13 Clinical Chemistry (Serum or Plasma)

Albumin	Glucose
ALP	Lactate dehydrogenase
ALT	Lipase
Amylase	Magnesium
AST	Phosphorus
Bicarbonate or carbon dioxide	Potassium
B type natriuretic peptide (BNP)[a]	Sodium
BUN or Urea depending on local practice	Total Bilirubin (A direct bilirubin should be obtained if total bilirubin is > ULN)
Calcium (total)	Total Protein
CA19-9	Troponin[a]
Chloride	TSH
Creatinine	T3 (reflex)
C-reactive protein	T4 (reflex)
Creatinine clearance (Cockcroft-Gault)	Uric acid
Gamma glutamyl transpeptidase	

[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.
Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate transaminase; BUN=blood urea nitrogen; CA19-9=carbohydrate antigen 19-9; T3=Free tri-iodothyronine; T4=free thyroxine; TSH=thyroid stimulating hormone; ULN=upper limit of normal; WBC=white blood cell.

NB. In case a participant shows an AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix H ‘Actions required in cases of increases in liver biochemistry and evaluation of Hy’s Law’, for further instructions.

Table 14 Haematology/Coagulation

Absolute (or differential, %) basophil count	Haematocrit
Absolute (or differential, %) eosinophil count	Hb
Absolute (or differential, %) lymphocyte count	INR
Absolute (or differential, %) monocyte count	Platelet count
Absolute (or differential, %) neutrophil count	Prothrombin
aPTT	WBC

Coagulation tests: If international normalised ratio is not available the sites may substitute a prothrombin time.
Note: For coagulation parameters, aPTT (either as a ratio or as an absolute value, in seconds) and international normalised ratio are to be assessed at baseline on Day 1 (unless all screening laboratory haematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.
Abbreviations: aPTT= activated partial thromboplastin time; Hb=haemoglobin; INR=international normalised ratio; WBC=white blood cell.

Table 15 Urinalysis (Dipstick)

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

Note: Urinalysis should be done at baseline (screening) and then as clinically indicated.

Table 16 Lipid Panel

Total Cholesterol	Triglyceride

Table 17 Pregnancy Test (Women of Childbearing Potential Only)

Urine hCG	Serum β-hCG

Serum β-hCG at screening only and if a urine hCG is equivocal or positive during the remainder of the study.
Abbreviations: β-hCG=beta-human chorionic gonadotropin; hCG=human chorionic gonadotropin.

8.3 Adverse Events and Serious Adverse Events

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix E.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events will be collected from time of signature of ICF throughout the treatment period and including the follow-up period (FUP-2).

SAEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

'The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- CTCAE grade/changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to study intervention
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix E 3 to the CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit or since you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in CSP-mandated laboratory values, vital signs and other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the study intervention and may require close monitoring and rapid communication by the investigator to 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.

8.3.6.1 CCI

CCI

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[redacted]

8.3.6.2 Adverse Events of Special Interest for Durvalumab

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 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. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other aetiologic causes of the imAE.

If the investigator has any questions regarding whether an AE is an imAE, the investigator should promptly contact the study physician.

AESIs/imAEs observed with anti-PD-L1/PD-1 agents such as durvalumab include:

- Pneumonitis
- Hepatitis
- Diarrhoea/colitis
- Intestinal perforation
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, type 1 diabetes mellitus, adrenal insufficiency, hyperthyroidism, and hypothyroidism)
- Nephritis
- Rash/dermatitis
- Myocarditis
- Myositis/polymyositis
- Pancreatitis
- Rare/less frequent imAEs including neuromuscular toxicities (eg, Guillain-Barre syndrome and myasthenia gravis) and encephalitis
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, haematological events, rheumatological events, vasculitis and non-infectious meningitis. It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs.

In addition, IRRs and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in in the TMGs (refer to TMGs Annex).

8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix H for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

Refer to TMGs for management of Hy's Law cases.

8.3.8 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.8.1 New Cancers

The development of a new cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the study intervention and have been identified after the participant's inclusion in the study. New metastatic lesion(s) of the participant's known cancer should not be reported as a new cancer.

8.3.8.2 Deaths

All deaths that occur during the study, including the CSP-defined follow-up period (FUP-2) must be reported as follows:

- Death clearly the result of disease progression should be reported and documented on the statement of death eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to disease progression, the AE causing the death must be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem (autopsy) may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to the sponsor within the usual timeframes (see Section 8.3.9).

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar**

days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

For further guidance on the definition of an SAE, see Appendix E 2.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference documents for definition of expectedness/listedness are the current AZD0171 and durvalumab IB's.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during exposure to study intervention, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose of study intervention.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 6 months after the last dose and as indicated by previous studies (pre-clinical and clinical) should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.11 Medication Error

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix E 4.

8.3.11.1 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix E 4.

8.3.11.2 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix E 4.

8.3.11.3 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix E 4.

8.4 Overdose

For this study, any dose of study intervention greater than those specified in the CSP will be considered an overdose. This may include a higher dose of study intervention or study intervention taken at the correct dose but for longer duration.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix F.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- 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 (Section 1.3).
- Individual sampling timepoints are provided in Table 18, Table 19, and Table 20 for AZD0171 and total LIF, Table 21 and Table 22 for durvalumab, and Table 23 and Table 24 for chemotherapy (gemcitabine and nab-paclitaxel).
- All sampling PK timepoints including end of infusion are relative to their respective study intervention infusion on the day of administration.
- Day 8 AZD0171 pre-dose PK sampling will be collected prior to study intervention administration.
- A single sample will be taken at the AZD0171 sampling timepoints which will be split into 2 samples for the individual analysis of AZD0171 PK and an aliquot for analysis of total LIF (PD).
- 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). Pre-dose PK samples matched to AZD0171 and durvalumab ADA samples will be collected for all participants.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor eg for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

- Serum samples will be used to analyse the PK of AZD0171, and durvalumab, and plasma samples will be used analyse the PK of gemcitabine, gemcitabine metabolite 2′,2′-difluoro-deoxyuridine (dFdU), and nab-paclitaxel. Samples collected for analyses of study intervention concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of study intervention concentration in serum or plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

Table 18 PK Sampling Timepoint Schedule for AZD0171 and Total LIF (PD) [a] (Safety Run-in: 10 to 12 Participants Only)

Cycle number	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Every Cycle from Cycle 5-11
Cycle number and cycle day	**C1 D1**	**C1 D8 [b]**	**C1 D15**	**C2 D1**	**C2 D8 [b]**	**C2 D15**	**C3 D1**	**C3 D8 [b]**	**C3 D15**	**C4 D1**	**C4 D8 [b]**	**C4 D15**	**C5-11 D1**
Safety run-in participants only [d]	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)		Pre-dose (within 90 min)	Pre-dose (within 90 min)		Pre-dose (within 90 min)
	EOI (± 15 min)		EOI (± 15 min)	EOI (± 15 min)		EOI (± 15 min)	EOI (± 15 min)		EOI (± 15 min)	EOI (± 15 min)		EOI (± 15 min)	EOI (± 15 min) Q3 cycles from C5-11 only
	1 hr post infusion ± 10 min									1 hr post infusion ± 10 min			
	3 hrs post infusion ± 15 min									3 hrs post infusion ± 15 min			
	6 hrs post infusion ± 30 min									6 hrs post infusion ± 30 min			
	24 hrs post-Day 1 end of infusion (± 4 hrs) [e]									24 hrs post-Day 1 end of infusion (± 4 hrs) [f]			

[a] Timings for collection of AZD0171 PK samples are relative to AZD0171 infusion.
[b] Day 8 AZD0171 pre-dose PK sample will be collected prior to chemotherapy administration.
[c] Intensive PK timepoints will be collected in the safety run-in participants only (first 10 to 12 participants).
[d] Pre-dose PK samples matched to ADA samples will be collected from all participants.
[e] This will be C1 D2.
[f] This will be C4 D2.
Abbreviations: C=cycle; D=Day; EOI=End of Infusion; hrs=hours; LIF=leukaemia inhibitory factor; min=minutes; PK=pharmacokinetics; Q3=every 3.

Table 19 PK Sampling Timepoint Schedule for AZD0171 and Total LIF (PD) [a] (First 40 Participants Only: Including Safety Run-in)

Cycle number	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Every Cycle from Cycle 5-11
Cycle number and cycle day	C1 D1	C1 D8 [b]	C1 D15	C2 D1	C2 D8 [b]	C2 D15	C3 D1	C3 D8 [b]	C3 D15	C4 D1	C4 D8 [b]	C4 D15	C5-11 D1
First 40 Participants Only [c,d] (Including safety run-in)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)	Pre-dose (within 90 min)		Pre-dose (within 90 min)	Pre-dose (within 90 min)		Pre-dose (within 90 min)
	EOI (± 15 min)		EOI (± 15 min)	EOI (± 15 min)		EOI (± 15 min)	EOI (± 15 min)		EOI (± 15 min)	EOI (± 15 min)		EOI (± 15 min)	EOI (± 15 min) Q3 cycles from C5-11 only

[a] Timings for collection of AZD0171 PK samples are relative to AZD0171 infusion.
[b] Day 8 AZD0171 pre-dose PK sample will be collected prior to chemotherapy administration.
[c] Non-intensive PK timepoints will be collected in the first 40 participants only (including the run-in participants, ie, 10 to 12 safety run-in participants plus 28-30 non-intensive participants).
[d] Pre-dose PK samples matched to ADA samples will be collected from all participants.
Abbreviations: C=cycle; D=Day; EOI=End of Infusion; LIF=leukaemia inhibitory factor; min=minutes; PK=pharmacokinetics; Q3=every 3.

Table 20 PK Sampling Timepoint Schedule for AZD0171 and Total LIF (PD) [a] (All Participants)

Cycle number	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Every Cycle from Cycle 5-11
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	C5-11 D1
All Participants[b,c]	Pre-dose (within 90 min)		Pre-dose (within 90 min)	Pre-dose (within 90 min)		Pre-dose (within 90 min)	Pre-dose (within 90 min)			Pre-dose (within 90 min)			Pre-dose (within 90 min)

[a] Timings for collection of AZD0171 PK samples are relative to AZD0171 infusion.
[b] Non-intensive pre-dose PK timepoints will be collected in all participants.
[c] Pre-dose PK samples matched to ADA samples will be collected from all participants.
Abbreviations: C=cycle; D=Day; LIF=leukaemia inhibitory factor; min=minutes; PK=pharmacokinetics.

Table 21 PK Sampling Timepoint Schedule for Durvalumab [a] (First 40 Participants Only: Including Safety Run-in)

Cycle number	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Q3 Cycles from Cycle 5-11
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	C5-11 D1
First 40 Participants Only [b, c] (Including safety run-in)	Pre-dose (within 90 min)			Pre-dose (within 90 min)			Pre-dose (within 90 min)			Pre-dose (within 90 min)			Pre-dose (within 90 min)
	EOI (± 15 min)			EOI (± 15 min)			EOI (± 15 min)			EOI (± 15 min)			EOI (± 15 min)

[a] Times for collection of durvalumab PK samples are relative to durvalumab infusion.
[b] Non-intensive PK timepoints will be collected in the first 40 participants only (including the run-in participants, ie, 10 to 12 safety run-in participants plus 28-30 non-intensive participants).
[c] Pre-dose PK samples matched to ADA samples will be collected from all participants.
Abbreviations: ADA=anti-drug antibody; C=cycle; D=Day; EOI=End of Infusion; min=minutes; PK=pharmacokinetics; Q3=every 3.

Table 22 PK Sampling Timepoint Schedule for Durvalumab [a] (All Participants)

Cycle number	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Q3 Cycles from Cycle 5-11
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	C5-11 D1
All Participants [b,c]	Pre-dose (within 90 min)			Pre-dose (within 90 min)			Pre-dose (within 90 min)			Pre-dose (within 90 min)			Pre-dose (within 90 min)

[a] Timings for collection of durvalumab PK samples are relative to durvalumab infusion.
[b] Non-intensive pre-dose PK timepoints will be collected in all participants.
[c] Pre-dose PK samples matched to ADA samples will be collected from all participants.
Abbreviations: C=cycle; D=Day; min=minutes; PK=pharmacokinetics; Q3=every 3.

Table 23 PK Sampling Timepoint Schedule for Chemotherapy [a] (Safety Run-in: 10 to 12 Participants Only)

Cycle number	Cycle 1			Cycle 2			Cycle 3			Cycle 4		
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**
Safety Run-in Participants Only [b]	Pre-dose (within 90 min)		Pre-dose (within 90 min)							Pre-dose (within 90 min)		Pre-dose (within 90 min)
	EOI (± 15 min)		EOI (± 15 min)							EOI (± 15 min)		EOI (± 15 min)
			1 hr post infusion ± 10 min									1 hr post infusion ± 10 min
			3 hrs post infusion ± 15 min									3 hrs post infusion ± 15 min
			6 hrs post infusion ± 30 min									6 hrs post infusion ± 30 min
			24 hrs post-Day 1 end of infusion (± 4 hrs) [c]									24 hrs post-Day 1 end of infusion (± 4 hrs) [d]

[a] Chemotherapy PK timepoint applies to each chemotherapy separately. PK samples for nab-paclitaxel should be collected relative to nab-paclitaxel infusion and all PK samples for gemcitabine should be collected relative to gemcitabine infusion.
[b] Intensive PK timepoints will be collected in the safety run-in participants only (first 10 to 12 participants).
[c] This will be C1 D16.
[d] This will be C4 D16.

Abbreviations: C=cycle; D=Day; EOI=End of Infusion; hrs=hours; min=minutes; PK=pharmacokinetics.

Table 24 PK Sampling Timepoint Schedule for Chemotherapy [a] (First 40 Participants Only: Including Safety Run-in)

Cycle number	Cycle 1			Cycle 2			Cycle 3			Cycle 4		
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**
First 40 Participants [b] (Including safety run-in)	Pre-dose (within 90 min)									Pre-dose (within 90 min)		
	EOI (± 15 min)									EOI (± 15 min)		

[a] Chemotherapy PK timepoint applies to each chemotherapy separately. PK samples for nab-paclitaxel should be collected relative to nab-paclitaxel infusion and all PK samples for gemcitabine should be collected relative to gemcitabine infusion.

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

Abbreviations: C=cycle; D=Day; EOI=End of Infusion; min=minutes; PK=pharmacokinetics.

8.5.2 Immunogenicity Assessments

Blood samples collected as per the SoA (Section 1.3) for determination of ADA in serum for AZD0171 and durvalumab will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

ADA samples may also be further tested for characterisation of the ADA response.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

Pharmacodynamic CCI will be used to inform the extent and duration of LIF and PD-L1 target inhibition following treatment with AZD0171 in combination with durvalumab and chemotherapy. PD CCI analyses will also be used to obtain assessment of the AZD0171 PK-PD relationship in participants and determine any retrospective correlations for response to study intervention.

8.5.3.1 Collection of Samples

The collection of blood based PD CCI samples and tumour samples will provide assessment of downstream effects of AZD0171 administration in combination with durvalumab and chemotherapy in participants. CCI

CCI

CCI

For storage, re-use and destruction of PD samples see Section 8.5 and Appendix F.

8.5.3.2 Collection of Serum and Plasma Samples for Circulating Soluble Factors

A peripheral blood sample will be collected to provide serum and plasma prior to administration of any study intervention for analysis of, but not limited to, baseline circulating LIF protein, total LIF, circulating levels of soluble factors and immune mediators of antitumour immune response to explore their association with treatment and clinical outcome. Blood samples are to be collected as detailed in the SoA (Section 1.3). Serum samples for total LIF will be collected at the same timepoints as AZD0171 PK samples (Section 8.5.1.1).

8.5.3.3 CCI

CCI

CCI [redacted]

8.5.3.4 Collection of Tumour Biopsies

All study participants must consent to provide an CCI [redacted] or the collection of a CCI [redacted] tumour biopsy specimen at screening. The screening tumour biopsy specimen must meet eligibility criteria for presence of tumour CD8+ T cell population based on central laboratory testing above a pre-specified cut-off (Section 5.1).

Paired screening and on-study tumour biopsy specimens with **sufficient and evaluable** tissue material are required from up to CCI participants on the study. Tumour biopsy specimens from the same lesion is preferable and may be from the primary (preferred) or metastatic tumour. In the event that a participant is eligible at study entry but paired on-study tumour biopsies are not medically feasible, and the required number of on-study biopsies has not been achieved, such a participant may continue to be evaluated for study entry with the sponsor's permission.

CCI [redacted] samples at screening from either primary or metastatic tumour will be accepted if performed during metastatic stage and tissue from the primary tumour is preferred. In case of multiple CCI [redacted], most recent biopsy to be sent.

If CCI [redacted] is not available or if the CCI [redacted] was taken over 3 months prior to consent, then participants must consent to the collection of a CCI [redacted] as part of screening prior to first dose of study intervention (Section 5.1). It is strongly recommended that shipment of tumour biopsy specimens to the central laboratory test facility should occur within 2 weeks of signed ICF.

Approximately CCI [redacted] sections from the archival tumour block are accepted if tumour blocks cannot be submitted, however tumour tissue blocks are preferred. Fine needle aspirates or bone decalcified samples are inadequate to establish participant eligibility. Where available, provision of a copy of the pathology report associated with the tumour sample is also required.

All study participants will have the opportunity to provide on-study tumour biopsy specimens per SoA (Section 1.3).

Once at least 20 paired screening and on-study tumour biopsy specimens with **sufficient and evaluable** tissue material have been collected, the sponsor will inform all investigative sites that further paired biopsies are no longer required to be collected.

Biopsies will be obtained at acceptable risk as judged by the investigator using low-risk procedures at screening and during study intervention. Collection timepoints can be found in the SoA (Section 1.3).

Consent for optional tumour biopsy specimen at disease progression may also be provided by

participants.

Tumour lesions planned for biopsy are to be target lesions (preferred though not required).

Core biopsies and archival tissues may be used for correlative studies such as but not limited to IHC, tumour mutation analysis, proteomic analysis, and immunodiversity.

Full details of collecting CCI, sample collection (CCI), processing, shipping and storage will be described in the Laboratory Manual.

8.6 CCI

8.6.1 CCI

CCI

8.6.2 CCI

CCI

CCI

8.7 CCI

CCI

CCI

CCI

CCI

8.8 Health Economics OR Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypotheses will be tested. A statistical estimation approach will be used with appropriate CIs determined to address the objectives described in Section 3.

9.2 Sample Size Determination

Approximately 370 participants will be screened/enrolled to achieve approximately 115 assigned to study intervention and up to approximately 115 evaluable participants.

Note: “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]

9.3 Populations for Analyses

The following populations are defined:

Table 25 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who signed the ICF.
Safety	All participants who receive any amount of investigational product.
ITT	All participants who receive any dose of study intervention.
Response Evaluable	All dosed participants who had measurable disease at baseline.
Interim Response Evaluable	All dosed participants who had measurable disease at baseline and who had first dose at least 17 weeks prior to data extract (where 17 is 2 × the protocol lead time between scans + 1 week to allow for a late assessment).

Population/Analysis set	Description
PK	All participants who received any amount of study intervention with at least 1 reportable PK measurement.
PD	All participants who received any amount of study intervention with at least 1 reportable PD measurement.
Immunogenicity	All participants who receive at least 1 dose of investigational product with at least 1 reportable immunogenicity assessment.

Abbreviations: AE=adverse event; ICF=informed consent form; ITT=intent-to-treat; PD=Pharmacodynamic; PK=pharmacokinetic.

9.4 Statistical Analyses

The SAP will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any deviations from the planned analysis will be described in an SAP addendum and justified in the final integrated CSR.

9.4.1 General Considerations

All statistical analyses will be performed by Parexel International Biostatistics or other designated third party providers, under the direction of the Biostatistics Group, AstraZeneca. Further details will be provided in the SAP. All statistical analyses presented in the CSP will be performed using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, US), version 9.4 or higher. Exploratory endpoint analyses may be reported outside of the CSR.

Data will be presented as defined in the SAP. Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum.

Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated based on the population total and by timepoint as appropriate.

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study intervention, and other CSP deviations) may be generated. More detail will be provided in the SAP.

9.4.2 Efficacy Analyses

The efficacy analyses of antitumour activity will be based on the response evaluable set (defined in Section 9.3). The ORR and DCR based on RECIST v1.1 will be summarised based

on the exact binomial distribution.

Time-to-event endpoints (DoR, PFS, and OS) will be analysed using the Kaplan-Meier method. Additional analyses of antitumour activity may be conducted in the safety analysis population. Additional details will be provided in the SAP. The following efficacy endpoints will be analysed.

9.4.2.1 Primary Endpoint

- The primary analysis will be performed after all dosed participants have had opportunity for 12 months survival follow-up or died, whichever is sooner.
- The primary efficacy endpoint is OS-12, defined as the proportion of participants alive/surviving at 12 months after initiation of study intervention. The Kaplan-Meier method to estimate the OS curve on the ITT analysis set, then the OS-12 estimate is estimated from curve that with 80% CI. The OS curve will be censored on the last date when participants are known to be alive.

9.4.2.2 Secondary Endpoints

Secondary efficacy endpoints based on RECIST v1.1 include ORR, DCR, DoR, PFS, PFS-4, and OS. Analysis sets to be used for each endpoint will be described in the SAP.

Objective Response Rate

Objective response rate will be assessed per RECIST v1.1 criteria. ORR is defined as the proportion of participants with a best overall response of confirmed CR or PR that occurs prior to the initiation of subsequent anti-cancer treatment and prior to progression, with the denominator defined as the number of participants in the response evaluable set.

The best overall response of CR or PR must be confirmed, which means a response of CR/PR is recorded at a 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.

The ORR and its 80% CI will be estimated using the exact binomial distribution and will be summarised.

Disease Control Rate

The DCR is defined as the percentage of participants with a best overall response of confirmed CR or PR, or who have SD maintained for 16 weeks from first dose, where 16 weeks is the DCR time point. DCR and its 80% CI will be calculated using the exact binomial distribution.

Duration of response

The DoR is defined as the time from the date of first documented response until the date of documented progression or death (in the absence of disease progression).

Duration of response will be measured for responding participants (participants with confirmed CR or confirmed PR) only. Detailed analysis and censoring rules for DoR will be specified in the SAP.

Overall Survival

OS is defined as the time from the start of treatment to the date of death due to any cause. 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.

OS will be analysed using the Kaplan-Meier method. Median OS will be estimated with 80% CI.

Progression Free Survival

PFS is defined as the time from the start of treatment until the date of objective disease progression or death (by any cause in the absence of progression), whichever is earlier, regardless of whether the participant withdraws from therapy or receives another anti-cancer therapy prior to progression. Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

The PFS time will always be 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 will be applied:

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

PFS will be analysed using the Kaplan-Meier method. Median PFS will be estimated with 80% CI.

Additionally, the proportion of participants alive and PFS-4 and its associated 80% CI will be estimated using the Kaplan-Meier method. Other landmark time points may similarly be estimated.

9.4.3 Safety Analyses

9.4.3.1 Primary Endpoint

Adverse Events

Adverse events will be coded using the most recent version of MedDRA that will have been released for execution at AZ/designee.

AEs will be presented for each treatment group by SOC, HLT and/or PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

AE summary tables will include only treatment-emergent AEs. AEs will be defined as treatment-emergent if they have an onset or worsen (by investigator report of a change in intensity/severity), during treatment until the last dose of any study intervention or the safety follow-up period, but prior to subsequent cancer therapy. AEs occurring outside this period will only be listed.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and BP)/ECG data will be performed for identification of OAEs. Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

Treatment-emergent:

The following events are considered treatment emergent:

- Adverse events with an onset date on or after first dose of study intervention and within 90 days after last dose of study intervention or up to the day prior to start of subsequent therapy, whichever comes first.
- Worsening of pre-existing events on or after first dose of study intervention and within 90 days after last dose of study intervention or up to the day prior to start of subsequent therapy, whichever comes first.

Immune Mediated Adverse Events:

Duration of exposure will be summarised.

Safety data including AEs, SAEs, laboratory evaluations and vital signs results will be summarised for all participants based on the safety analysis set. Summary statistics will be

provided for AEs, imAEs, including AESIs, SAEs, and AE grade (severity) and relationship to study interventions (AZD0171, durvalumab, and chemotherapy), clinical laboratory parameters, ECGs, and vital signs. AEs will be graded according to NCI CTCAE v5.0 and described by system organ class and preferred term using MedDRA. Laboratory abnormalities with toxicity grades according to the NCI CTCAE v5.0 will be derived and summarised. Details of any deaths will be listed for all participants. Graphical presentations of safety data will be presented as appropriate. Further details will be provided in the SAP.

Descriptive statistics will be provided for the clinical laboratory results and changes from baseline by scheduled time of evaluation and by treatment including EOT visit as well as for the maximum and minimum post-baseline values.

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of study intervention. Details are described in the SAP.

9.4.4 Immunogenicity

9.4.4.1 Secondary Endpoint

All participants who receive at least 1 dose of IMP with at least 1 reportable immunogenicity assessment will be evaluated.

The immunogenic potential of AZD0171 and durvalumab will be assessed by summarising the number and percentage of participants who develop detectable ADAs. The impact of ADAs on PK, PD and safety will be assessed if data allow. Samples will be collected for potentially evaluating the neutralising capacity of ADAs in the future.

9.4.5 Pharmacokinetic

9.4.5.1 Secondary Endpoint

All participants who receive any amount of study intervention with at least 1 reportable PK measurement will be evaluated.

Pharmacokinetic analyses will be performed using the PK analysis set. Plasma concentrations for individual AZD0171, durvalumab and chemotherapies and/or their metabolites will be tabulated along with descriptive statistics. Non-compartmental PK data analysis will be performed from each study intervention with scheduled PK sample collection where data allow. Relevant descriptive statistics of non-compartmental PK parameters will be provided and will include: C_{max}, AUC, CL, and terminal elimination $t_{1/2}$.

9.4.5.2 Exploratory Endpoint

CCI [redacted].

CCI [redacted]

presented separately from the main CSR.

9.4.6 Pharmacodynamic

Analyses will be performed using the PD analysis population.

9.4.6.1 Secondary Endpoint

Tissue obtained as part of the screening procedure and mandatory/optional biopsies obtained during treatment will be assessed for CD8+ T cell tumour infiltration. Descriptive statistics will be used to describe participant and treatment specific changes from baseline. Serum CA19-9 and total LIF may be similarly analysed.

9.4.6.2 Exploratory Endpoints

CCI

CCI

CCI

CCI

9.4.7 CCI

9.4.7.1 CCI

CCI

9.5 Interim Analyses

An analysis of ORR will be performed, without pausing enrolment, after approximately 40 dosed participants have had the opportunity to complete 2 post-baseline scans. It is recommended that further recruitment to the study would be stopped if there is ≤ 10% chance that the ORR is at the TV or above.

Data for other endpoints may also be reviewed at time of this interim analysis.

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committee

Not applicable.

An 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. Additional safety reviews may be conducted at the discretion of the SRC.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the CSP and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The CSP, CSP amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the CSP will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- In the European Union, the Sponsor will comply with safety reporting requirements, and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to IMP will be reported to the Eudra Vigilance database within the required regulatory timelines.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened as defined in Section 5.4 are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

Potential Changes to Informed Consent During the COVID-19 Outbreak

General Principles

The rights, safety, and wellbeing of the study participants are the most important considerations and should prevail over interests of science and society. All informed consent activities must follow ICH GCP; the CSP; and local laws, regulations, and guidance. Prospective CSP waivers with respect to enrolment remain unacceptable. Participants should not be included in studies without written informed consent according to national laws and regulations and proper eligibility assessment.

The reconsent process described in this appendix must be adopted only at sites/countries affected by the COVID-19 outbreak where reaching the site means placing the study participant under unnecessary risk. The described process does not overrule local laws, regulations and guidance; where differences arise, the latter must be followed.

If the need for re-consenting study participants arises, visiting the investigator sites for the sole purpose of obtaining reconsent should be avoided.

Any validated and secure electronic system already used in the study for obtaining informed consent can be used as per usual practice and if in compliance with local regulations.

Process for Reconsent of Study Participants at Sites Affected by the COVID-19 Outbreak

Before reconsent is obtained, the approved updated participant information sheet and consent

form should be provided to study participants by email. If the study participant is not able to receive emails, courier or mail should be used.

Verbal consent via phone or teleconference is allowed.

If possible, verbal consent should be supplemented with email confirmation. The investigator should emphasise that study participants should only use email to confirm their ICF consent and that the participant should not include any sensitive personal identifier (eg, date of birth, social security number) or medical information including AEs.

Please note: Study participants should not sign the document at home after giving verbal consent. The phone call or teleconference should be informative. The document will be signed and filed with the participant's source data once the study participant is able to attend the site. Under no circumstances should the study participant scan and send the document back via email.

Verbal consent and print-out of the email confirmation (if available and once possible) must be documented by the investigator or delegate (if applicable) in the study participant's medical records.

Documentation should include details on when the contact took place, the reason why the study participant could not reach the site, any important details of the consenting call/concerns raised, and any questions raised (especially on safety measures) by the study participant and that these were answered satisfactorily by the site consenting party.

At the earliest possible occasion, consent must be documented via standard consent process. This would not apply if the study participant is lost to follow-up, dies, or the study ends before the COVID-19 outbreak is over. In this case the reason why the study participant did not sign the document in person has to be documented in the study participant's medical records.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).
- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is when the first participant consents to participate in the study and will be the study start date.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

AstraZeneca reserves the right to temporarily suspend or permanently terminate this study or components of the study at any time. The reasons for temporarily suspending or permanently terminating the study may include, but are not limited to the following:

Fatal event deemed related to study therapy (probable or certain causality after full etiological work-up). This will also result in a comprehensive review of safety.

Unexpected and life-threatening events deemed related to study therapy.

Sponsor decision that the study participants are placed at undue safety risk.

Participant enrolment is unsatisfactory.

Noncompliance that might significantly jeopardize the validity or integrity of the study.

Sponsor decision to terminate development of the study intervention.

If AstraZeneca determines that temporary suspension or permanent termination of the study or components of the study is required, AstraZeneca will discuss the reasons for taking such action with all participating Investigators. When feasible, AstraZeneca will provide advance notice to all participating Investigators of the impending action.

If the study or components of the study are suspended or terminated for safety reasons, AstraZeneca will promptly inform all Investigators and/or institutions conducting the study. AstraZeneca will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study or components of the study is suspended for safety reasons and it is deemed appropriate by AstraZeneca to resume the study or components of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A 11 Regulatory Reporting Requirements for Serious Breaches

Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.

- A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

- AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

The investigator should have a process in place to ensure that:

- O The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

Appendix B Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the Sponsor.

B 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on-site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Consent for the alternative means of carrying our visits and assessments will be obtained at study entry.

B 2 Rescreening of Participants to Reconfirm Study Eligibility

Rescreening for screen failure due to study disruption can be performed in previously screened participants; as defined in Section 5.4. Prior to rescreening, the investigator should confirm with the designated study physician.

B 3 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events and concomitant medications to be reported and documented.

B 4 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified healthcare professional from the study site or third party vendor service in the source documents, or by the participant themselves.

Appendix C Contraception Requirements

Contraception requirements for this study are as follows.

C 1 Women of Childbearing Potential

Please note, women of childbearing potential are defined as those who are not either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months prior to the planned date of first dose of study intervention without an alternative medical cause. The following age-specific requirements apply:

- Women < 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal replacement therapy and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal replacement therapy.

A highly effective method of contraception is defined as one that can achieve a failure rate of < 1% per year when used consistently and correctly.

C 2 Contraceptive Methods

The highly effective methods of contraception are described in the table below.

Highly Effective Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS)[a] • Bilateral tubal occlusion • Vasectomised partner[b] • Sexual abstinence[c]	Combined (oestrogen and progestogen containing hormonal contraception) • Oral (combined pill) • Injectable • Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation[d] • Injectable • Implantable • Intravaginal

[a] This is also considered a hormonal method.
[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant. However, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method.

Appendix D Response Evaluation Criteria in Solid Tumours Version 1.1

Measurability of Tumour Lesions

Tumour lesions will be categorised as follows:

- **Measurable Lesions** - Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
  - 10 mm calliper measurement by clinical examination (when superficial).
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions** - Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.
- **Target Lesions** - At baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be 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 should be selected.
- **Non-target Lesions** - It is possible to record multiple non-target lesions involving the same organ as a single item (eg, “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).
- **New Lesions** - Though only certain new lesion measurements will be included in the tumour burden, all new lesions that can be accurately measured should be recorded. Other new lesions will be included into the non-tumour burden.

RECIST Version 1.1 Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR)** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response (PR)** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progressive disease.)
- **Stable Disease (SD)** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response (CR)** - Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-complete response/Non-progressive disease (Non-CR/Non-progressive disease)** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
- **Progressive Disease** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see Section 7.1). In the absence of measurable disease, change in nonmeasurable disease comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localised to widespread.

Appearance of New Lesions

The appearance of new lesions is considered progressive disease according to RECIST version 1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions can nonetheless derive clinical benefit (Borghaei et al, 2015).

Evaluation of Overall Response

For the overall response based on RECIST version 1.1, confirmation of CR and PR is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. A confirmatory scan will also be required after an initial assessment of progressive disease for the purpose of managing treatment. If a participant discontinues the study due to progressive disease and begins another treatment, a confirmatory scan is not required. Treatment of participants may continue between the initial assessment of progressive disease and confirmation of progressive disease (which is not required by RECIST version 1.1). In the absence of clinical deterioration, such modifications to the RECIST may discourage the early discontinuation of treatment and provide a more complete evaluation of study therapy antitumour activity than would be seen with conventional response criteria.

Overall responses for all possible combinations of tumour responses in target and non-target lesions with or without the appearance of new lesions are provided below.

Evaluation of Overall Response using RECIST v1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
No target lesion[a]	Complete response	No	Complete response
Complete response	Not evaluable[b]	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion)[b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion)[b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion[a]	Not all evaluated	No	Not evaluable
No target lesion[a]	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion[a]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion[a]	Any	Yes	Progressive disease

[a] Defined as no target lesion at baseline.
[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.
Abbreviations: RECIST=Response Evaluation Criteria in Solid Tumours; v=version.
Reference: Eisenhauer et al, 2009.

Appendix E Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

E 1 Definition of Adverse Events

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 (for example 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.

E 2 Definitions of Serious Adverse Events

An SAE is an AE occurring during any study period (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent 1 of the outcomes listed above.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the study intervention under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the study intervention would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix E 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix E 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix E 2.

The grading scales found in the revised NCI CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

E 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

E 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion

- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that do not require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix F Handling of Human Biological Samples

F 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

F 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site is notified.

F 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content

Appendix G CCI

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Appendix H Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

H 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

H 2 Definitions

Potential Hy's Law
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × ULN **together with** Total Bilirubin (TBL) ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the

same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

H 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local Laboratories Being Used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Section H 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

H 4 Follow-up

H 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

H 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (see Section H 6)
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician.
  - Complete the 3 Liver eCRF Modules as information becomes available

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

H 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF

- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

H 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants with liver metastases who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on study intervention occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the participants' condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required

– If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section H 4.2

H 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study intervention and at their first on study intervention visit as described in Section 6 of this Appendix?

If **No**: follow the process described in Section H 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met.

- If there is no significant change no action is required
- If there is a significant change[#] follow the process described in Section H 4.2 for reporting PHL as an SAE

[#] **A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

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Appendix I National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognise 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalised hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
2. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
3. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
4. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
5. Involvement of the skin-mucosal tissue (eg, generalised hives, itch-flush, swollen lips-tongue-uvula).
6. Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
7. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
8. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
9. Reduced BP after exposure to known allergen for that participant (minutes to several hours):
10. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that participant’s baseline.

Reference: Sampson et al, 2006.

Appendix J Abbreviations

Abbreviation or special term	Explanation
1L	first line
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AST	aspartate aminotransferase/transaminase
AUC	area under the concentration-time curve
BP	blood pressure
BRCA	breast cancer gene
CA19–9	carbohydrate antigen 19–9
CD	cluster of differentiation
CD8+	cluster of differentiation 8
CFR	Code of Federal Regulations
CI	confidence interval
CL	Clearance
C_{max}	maximum observed concentration;
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CR	complete response
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCO	Data cut-off
DCR	disease control rate
DILI	Drug Induced Liver Injury
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response

Abbreviation or special term	Explanation
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EOI	end of infusion
EOT	end of treatment
ESMO	European Society for Medical Oncology
FDA	United States Food and Drug Administration
CCI	CCI
FOLFIRINOX	folinic acid, fluorouracil, irinotecan, oxaliplatin
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
gp130	glycoprotein 130
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency viruses
HL	Hy's Law
HLT	higher level term
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFNγ	interferon-gamma
IgG1κ	immunoglobulin G1 kappa
IHC	Immunohistochemistry
IL6	interleukin 6
ILD	interstitial lung disease
imAE	immune mediated adverse events
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRR	infusion-related reactions

Abbreviation or special term	Explanation
IV	Intravenous
IWRS	Interactive Web Response Systems
LIF	leukaemia inhibitory factor
LRV	lower reference value
mAbs	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
mPDAC	metastatic pancreatic ductal adenocarcinoma
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
OAE	other adverse event
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	median overall survival
OS-12	overall survival at 12 months
PCR	polymerase chain reaction
PD-1	programmed cell death protein 1
PDAC	pancreatic ductal adenocarcinoma
PD	pharmacodynamic(s)
PD-L1	programmed death-ligand 1
PEF	peak expiratory flow
PHL	Potential Hy's Law
PI	Principal investigator
PID	participant identification number
PK	pharmacokinetic(s)
PFS	median progression free survival
PR	partial response
PT	preferred term
Q1W	every week
Q2W	every 2 weeks
Q3	every 3
Q3W	every 3 weeks

Abbreviation or special term	Explanation
Q4W	every 4 weeks
Q8W	every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	ribonucleic acid;
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SoA	Schedule of Activities
SOC	system organ class
SRC	Safety Review Committee
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse events
TMG	toxicity management guidance
TV	target value
ULN	upper limit of normal
US(A)	United States (of America)
WOCBP	woman of childbearing potential
YAP1	yes1 associated transcriptional regulator

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