Statistical Analysis Plan	
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A Phase IB/II, 2-Stage, Open-label, Multicenter Study to Determine the Efficacy and Safety of Durvalumab (MEDI4736) + Paclitaxel and Durvalumab (MEDI4736) in Combination With Novel Oncology Therapies With or Without Paclitaxel for First-line Metastatic Triple Negative Breast Cancer

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
1L	First-line
ADA	Anti-drug antibody
AE	Adverse event
AEPI	Adverse events of possible interest
AESI	Adverse events of special interest
AJCC	American Joint Committee on Cancer
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
bid	Twice daily
BMI	Body mass index
BoR	Best objective response
CAP	College of American Pathologists
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse event
CCI [redacted]	
Dato-DXd	Datopotamab deruxtecan; DS-1062a
DCO	Data cut-off
DNA	Deoxyribonucleic acid
DLT	Dose-limiting toxicity
DoR	Duration of response
DS8201a	Trastuzumab deruxtecan; T-DXd
Durva	Durvalumab
ECG	Electrocardiogram
ECHO	Echocardiograms

Abbreviation or special term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FAS	Full analysis set
H&E	Hematoxylin and eosin stain
HER2	Human epidermal growth factor receptor 2
ICF	Informed consent form
IHC	Immunohistochemistry
imAE	Immune Mediated Adverse Events
INR	International normalization ratio
IP	Investigational product
IPD	Important protocol deviation
IRT	Interactive Response Technology
LD	Longest diameter
LVEF	Left ventricular ejection fraction
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
CCI	
MUGA	Multiple gated acquisition scans
NA	Not applicable
NCI	National Cancer Institute
NE	Not evaluable
NTL	Non-target lesions
ORR	Objective response rate
OS	Overall survival
Pac	Paclitaxel
PD	Progressive disease
PD-L1	Programmed cell death ligand 1
PFS	Progression free survival
PIK3CA	Phosphoinositide-3-kinase, catalytic, alpha polypeptide
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PT	Preferred term
q1w	Every 1 week
q2w	Every 2 weeks

Abbreviation or special term	Explanation
q4w	Every 4 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase II dose
RTSM	Randomization and Trial Supply Management System
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
SRC	Safety review committee
TEAE	Treatment emergent adverse event
CCI	
TL	Target lesion
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
WHO-DD	World Health Organisation Drug Dictionary

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with CSP? Y (version) / N / NA	Rationale
Primary or secondary endpoints	02 Jul. 2020	Language describing the primary, secondary and exploratory objectives have been updated to allow for the changes to the treatment arms. Applies to Tables 1, 2 and 3	Y (v4.0)	To align with CSP
	02 Jul. 2020	Added exposure to the list of endpoints/variables for the primary objective. Applies to Table 1	Y (v4.0)	To align with CSP and improve previous intent
Derivation of primary or secondary endpoints	22 Aug. 2019	Removed text stating that confirmatory scans are needed for PD. Applies to Section 3.1	Y (v3.0)	To align with CSP
	22 Aug. 2019	Updated the time windowing for the baseline assessment. Applies to Table 13	NA	To provide clarity when programming and applying visit windows
	22 Aug. 2019	Modified text on missing AE stop dates and missing birth dates. Applies to Section 3.6.3	NA	To align with PHUSE guidance
	22 Aug. 2019	Removed reference to 30 days after last dose and added text to indicate data will be mapped according to visit windowing rules. Applies to Sections 4.4.5, 4.4.6 and 4.4.7	NA	Modified to prevent hard cut-off of safety data in the exclusion of valid safety assessments
	22 Aug. 2019	Language for two missed visits rule for RECIST assessments updated. Applies to Section 3.2.2	NA	Updated to align with AZ standard Oncology SAP guidance
	08 Oct. 2019	Modified text on recording the presence of new lesions and therefore also overall visit response. Applies to section 3.1.1.2 and Table 11	NA	To improve previous intent
	O8 Oct. 2019	Modified text on data used to calculate efficacy variables. Applies to Section 3.2	NA	To improve previous intent
	08 Oct. 2019	Text on analysis visits and visit windows and definition of baseline updated. Applies to Section 3.6.2, Table 13	NA	Updated to make it clear Table 13 refers to Arm 1 only, correct the analysis visits and windows presented in the table, clarify which baseline variables can be averaged

02 Jul. 2020	Added “which is subsequently confirmed” to the definition of the DoR secondary endpoint and modified the language defining the variables/endpoints for the PK objective. Applies to Table 2	Y (v4.0)	To align with CSP and improve previous intent
02 Jul. 2020	Added text to add clarity and CCI to the endpoints/variables for the molecular/biological response objective. Applies to Table 3	Y (v4.0)	To align with CSP
02 Jul. 2020	Modified the rules to derive BoR of SD, PD and NE to allow for the inclusion of Arm 6. Applies to Section 3.2.4	Y(v4.0)	To align with CSP
02 Jul. 2020	Modified the text on Overall Survival to clarify what actions will be taken during a survival sweep and in situations where a sweep is not performed. Applies to Section 3.2	NA	To improve previous intent
02 Jul. 2020	Modified the definition of TEAE to correct the definition and use consistent language. Applies to Section 3.3	NA	To improve previous intent
02 Jul. 2020	Added text on AESI and AEPIs to the SAP. Applies to Sections 3.3 and 4.4	NA	To improve previous intent and align with AZ standard guidance
02 Jul. 2020	Removed text indicating data will be mapped according to visit windowing rules. And replaced with reference to 30 days after last dose. Applies to Sections 4.4.5, 4.4.6 and 4.4.7	NA	Modified to ensure hard cut-off of safety data
10 Sep.2020	Updated time to event endpoints (ORR, OS, PFS) to refer to time from first dose rather than time from randomization. Applies to Sections 3.2.1, 3.2.2, 3.2.5 and Table 2	Y(v5.0)	To align with CSP
10 Sep. 2020	Updated the BoR Section to align with changes to the ORR section. Applies to Section 3.2.4	Y(v5.0)	To align with CSP
10 Sep. 2020	Updated the definition of baseline for efficacy variable to accommodate the change to time from first dose definition. Applies to Section 3.2.6	Y(v5.0)	To align with CSP

	01 Nov. 2021	Objective response rate definitions in Section 3.2.1 updated to be consistent with the protocol and other efficacy definitions	Y(v7.0)	To align with CSP
	04 Oct. 2023	Added ophthalmologic assessments to endpoints, applies to Section 1.1.1/1.2.2	Y (v10.0)	To align with CSP
	04 Oct. 2023	Added summary of ophthalmologic assessments to section 4.4.10		
Editorial	22 Aug. 2019	Language for two missed visits rule for RECIST assessments updated. Applies to Section 3.2.2	NA	To improve clarity and align with TA SAP
	22 Aug. 2019	Rule for the imputation of best percentage change in tumor size. Applies to Section 3.2.6	NA	To improve clarity and align with TA SAP
	22 Aug.2019	List of severe AEs considered to be DLTs updated. Applies to Section 3.3.3	Y (v3.0)	To align with CSP
	22 Aug 2019	Calculation for actual exposure modified. Applies to Section 3.3.4	NA	To improve clarity
	22 Aug. 2019	Modified text on immunogenicity variables. Applies to Section 3.5.3	NA	To improve clarity
	22 Aug. 2019	Corrected the analysis sets that are to be used for ADA and PK data. Applies to Sections 4.1 and 4.6, Table 7	Y (v3.0)	To improve clarity
	22 Aug. 2019	Added further details on how prior and concomitant medications will be summarized. Applies to Section 4.2.4	NA	To improve clarity
	22 Aug. 2019	Modified text on AE and AESI summaries. Applies to Section 4.4.1	NA	To improve clarity
	22 Aug. 2019	Text on BoR added. Applies to Sections 3 and 4	Y (v3.0)	To align with CSP
	22 Aug. 2019	Replaced all occurrences of “patient(s)” with “subject(s)”. Applies throughout	NA	To align with ICH E6 guidance
	22 Aug. 2019	Updated version number of the CSP from 1 to 3. Applies Section 1.0	Y (v3.0)	To align with CSP
	22 Aug. 2019	Number of subjects to be recruited to each of the novel treatment combinations (Arms 2, 4 and 5) has been increased from 20 to 30. Text dependent on sample size updated. Applies to Sections 1.2 and 1,3, Table 6	Y (v3.0)	To align with CSP
	22 Aug. 2019	Removed reference to NHP. Applies to Section 2.2	NA	To align with other durvalumab studies
	22 Aug. 2019	Replaced “randomized” in Deviation 2 with “assigned”. Applied to Section 2.2	NA	To align with language used throughout the SAP
	22 Aug. 2019	Replaced MedDRA version number with “latest or current	NA	To align with language used in

	version". Applies to Sections 3.3.1 and 4.4.1		other durvalumab studies
22 Aug. 2019	Removed paclitaxel from the list of treatments for which dose intensity will be calculated. Applies to Section 3.3.4.3	NA	To improve clarity
22 Aug. 2019	Added text to clarify what constitutes a dose for the bid treatment capivasertib. Applies to Section 3.3.4.3	NA	To improve clarity
22 Aug. 2019	Updated wording on prior and concomitant medications. Applies to Section 3.5.2	NA	To align with TA SAP
22 Aug. 2019	Changed "subjects randomized to treatment" to "randomized subjects". Applies to Section 4.2.2	NA	To improve clarity
22 Aug. 2019	Replaced occurrences of "causally related" to "possibly related". Applies to Section 4.4.1	NA	To align with TA SAP
22 Aug. 2019	Removed reference to the edition of the AJCC manual	NA	Removed to allow for updated versions
07 Oct. 2019	Removed "allocated to treatment" in definition of SAF. Applies to Section 2.1.3	NA	To improve clarity
07 Oct. 2019	Modified text on the ADA-evaluable set and added abbreviation SAF as Safety Analysis Set. Applies to Section 2.1.3 and 3.5.3	NA	To improve clarity
07 Oct. 2019	Definition of PK analysis set updated. Applies to Section 2.1.4	NA	Updated to allow exclusion of subjects whose data violates or deviates from the CSP
07 Oct. 2019	Details added to the study design for sample size and to clarify what happens to subjects in screening if arms are closed for DLT evaluation. Applies to Section 1.2,	NA	To clarify previous intent of study process
07 Oct. 2019	Details added to clarify dose modifications following the DLT period. Applies to Table 5	Y (v3.0)	To align with CSP
07 Oct. 2019	Number of subjects text modified. Applies to Section 1.3	Y (v3.0)	To align with CSP
07 Oct. 2019	Occurrence of "allocated" replaced with "assigned". Applies to Section 2.1.2	NA	To align with language used in the rest of the SAP
08 Oct. 2019	Language for violations and deviations updated. Applies to Section 2.2	NA	To align with other durvalumab studies
08 Oct. 2019	Added text related to PK violations and monitoring of important deviations. Applies to Sections 2.2 and 2.3	NA	Modified to align with updates to the IPD process and guidance

08 Oct. 2019	Added full text for the PD abbreviation. Applies to Section 3.1.1	NA	To improve clarity
08 Oct. 2019	Added RECIST version number to BoR text. Applies to Section 3.2.4	NA	To improve clarity
08 Oct. 2019	Modified text on when survival calls will be made. Applies to Section 3.2.5	NA	To improve clarity
08 Oct. 2019	Added text on what happens to subjects who are not evaluable for toxicity. Applies to Section 3.3.3	NA	To improve clarity
08 Oct. 2019	Modified the treatments that are going to be summarized by number of doses/infusions. Applies to Section 3.3.4	NA	To improve clarity
08 Oct. 2019	Added text for deriving actual dose administered for infusion related medications. Applies to Section 3.3.4	NA	To improve clarity
08 Oct. 2019	Changed the timeframe for DCO for the final analysis from 2 years to 2.5 years	Y (v3.0)	To align with CSP
08 Oct. 2019	Removed redundant text from General principles. Applies to Section 4.1	NA	To improve clarity
08 Oct. 2019	Fixed typos. Applies to Sections 3.3.5, 4.2.4, 4.3.1, 4.3.4, 4.3.5	NA	To improve clarity
08 Oct. 2019	Removed repeated text on RECIST assessments. Applies to Section 3.1.1	NA	To improve clarity
08 Oct. 2019	Modified text to clarify visit responses when TL data is missing. Applies to Section 3.1.1.1	NA	To clarify wording and align with TA SAP
08 Oct. 2019	Modified text on scheduled frequency of RECIST assessments and 2-missed visits. Applies to Section 3.2.2	NA	To improve clarity
08 Oct. 2019	Replaced “already” with “subsequently” in derivation of duration of response. Applies to Section 3.2.3	NA	To clarify wording and align with TA SAP
08 Oct. 2019	Added text to say that CR or PR must be confirmed. Applies to section 3.2.4	NA	To align with TA SAP
08 Oct. 2019	Removed reference to ICR for BoR and replaced with RECIST 1.1. Applies to Section 3.2.4	NA	To improve clarity
08 Oct. 2019	Amended the definition of best percentage change. Applies to Section 3.2.6	NA	To align with TA SAP
08 Oct 2019	Modified summaries of ORR to include responses relative to the	NA	To improve clarity

	start of subsequent therapy. Applies to Section 3.2.1		
09 Oct. 2019	Modified text on Hy's law. Applies to Section 4.4.4	Y (v3.0)	To improve clarity
09 Oct. 2019	Modified text on Liver biochemistry results. Applies to Section 4.4.4	NA	To improve clarity
09 Oct. 2019	Modified text on analyses of efficacy to indicate censoring of subjects when RECIST assessments are no longer collected. Applies to Section 4.3	NA	To improve clarity
09 Oct. 2019	Modified summaries of ECOG. Applies to Section 4.4.7	NA	To improve clarity
09 Oct. 2019	Modified summaries of percentage change in tumor size and added example of window. Applies to Section 4.3.5	NA	To improve clarity
09 Oct. 2019	Modified the text on Biomarker analysis. Applies to section 4.7.1	NA	To improve clarity
09 Oct. 2019	Modified text on actual exposure, actual exposure derivation and dose delays to indicate what happens for drugs with intermittent dosing and to reference Section 8.2. Applies to Section 3.3.4	NA	To improve clarity
09 Oct. 2019	Modified the list of laboratory variables that are being assessed and moved the definition of ALC to Section 3.3.6. Applies to Section 4.4.4	Y (v3.0)	To improve clarity and align with CSP
06 Nov. 2019	Added text for Section 8.2 with examples exposure calculations	NA	To improve clarity
06 Nov. 2019	Added text on the cut-off used for truncated AE summaries. Applies to Section 4.4.1	NA	To improve clarity
02 Jul. 2020	Title modified to allow for the new arms	Y (v4.0)	To align with CSP
02 Jul. 2020	Modified the list of abbreviations to account for terms added or removed	NA	To improve previous intent
02 Jul. 2020	Study details, dosing regimens and descriptions of the safety run-in have been updated to allow for the removal of Arm 4 and the addition of Arm 6. Applies to Sections 1.0, 1.2, Table 4 Table 5	Y (v4.0)	To align with CSP
02 Jul. 2020	Updated overview of study design diagram and footnotes to accommodate the changes to the treatment arms. Applies to Figure 1	Y (v4.0)	To align with CSP

02 Jul. 2020	Replaced “triplet” with “novel treatment”. Applies throughout	Y (v4.0)	To align with CSP
02 Jul. 2020	Added details of the recruitment criteria for Arm 6. Applies to Section 1.2	Y (v4.0)	To align with CSP
02 Jul. 2020	Updated sample text to account for changes in treatment arms. Applies to Section 1.3	Y (v4.0)	To align with CSP
02 Jul. 2020	Modified presentation of i.e. and e.g. for consistency. Applies throughout	Y (v4.0)	To improve previous intent
02 Jul. 2020	Updated the language around ADA-evaluable set and PK analysis set to clarify that baseline and post-baseline results must be for the same agent. Applies to Sections 2.1.3 and 2.1.4	NA	To improve previous intent
02 Jul. 2020	Modified definition of on-treatment for AEs to allow for Arm 6 addition. Applies throughout	Y (v4.0)	To align with CSP
02 Jul. 2020	Reference to Section 8.3.13 of CSP has been changed to Section 8.3.14 in order to capture new CSP section numbering. Applies to Section 3.3.2	Y (v4.0)	To align with CSP
02 Jul. 2020	Updated text on DLTs and DLT-evaluable to incorporate new treatment Arms. Also added Section 3.3.3.1 for DLTs and Section 3.3.3.2 for DETs. Applies to Sections 1.2 and 3.3.3	Y (v4.0)	To align with CSP and improve previous intent
02 Jul. 2020	Updated text on exposure to incorporate changes to treatment arms. Applies to Sections 3.3.4, 8.1, 8.3 and Table 12	Y (v4.0)	To align with CSP
02 Jul. 2020	Modified text on scheduled frequency of RECIST assessments and 2-missed visits. Applies to Sections 3.1 and 3.2.2	Y (v4.0)	To align with CSP
02 Jul. 2020	Added DETs to the list of AESIs. Applies to Section 4.4.1	NA	To improve previous intent
02 Jul. 2020	Added text to accommodate changes in the paclitaxel dosing regimen for Arm 2. Applies to Section 1.2	Y (v4.0)	To align with CSP
02 Jul. 2020	Modified the text on the dictionaries that will be used for prior and concomitant medications. Applies to Sections 3.5.2 and 4.2.4	NA	To improve previous intent
02 Jul. 2020	Added clarity on what will be done for ADA-results recorded as categorical variables and corrected text on what summaries will be	NA	To improve previous intent

	presented for each treatment arm. Applies to Section 4.6		
02 Jul. 2020	Added text to clarify what windowing will be done when we have two visits equidistant from the scheduled day. Applies to Section 4.3.5	NA	To improve previous intent
02 Jul. 2020	Modified text on Analysis of safety to include changes to treatment arms. Applies to Section 4.4	Y (v4.0)	To align with CSP
02 Jul. 2020	Updated the list of Coagulation laboratory assessments resulting from treatment arm changes. Applies to Section 4.4.4	Y (v4.0)	To align with CSP
02 Jul. 2020	Corrected the figures showing how the dosing interval is received for Arm 6. Applies to Section 8.1	NA	To improve previous intent
02 Jul. 2020	Added some extra information to the total duration of dose delays calculations. Applies to Section 8.3.2.1	NA	To improve previous intent
02 Jul. 2020	Removed the text on total duration of dose delays for paclitaxel from Section 8.3.2.2 and added it to the start of Section 8.3.2.	NA	To improve previous intent
02 Jul. 2020	Removed the text referring to PD-L1 and immune cell expression may be reported in the CSR as this was not consistent with the CSP. Applies to section 4.7.1	Y (v4.0)	To align with CSP
10 Sep. 2020	Added text to specify that T-DXd can also be used to refer to DS-8201a. Applies to Sections 1 and 1.2	Y(v5.0)	To align with CSP
10 Sep. 2020	Updated the overview of study design diagram to reflect the changes in text	Y(v5.0)	To align with CSP
10 Sep. 2020	Added text to clarify that there will be assessments of efficacy using the CCI Applies to Section 1.2	Y(v5.0)	To align with CSP
10 Sep. 2020	Updated the language around recruitment to the different cohorts. Also modified text on efficacy assessments to be performed by removing "confirmed" from ORR and adding "at least" to the number of treatment responses required. Applies to Section 1.2	Y(v5.0)	To align with CSP
10 Sep. 2020	Modified the text on sample size to account for the CCI CCI Applies to Section 1.3	Y(v5.0)	To align with CSP
10 Sep. 2020	Modified the text on analysis populations to include the	Y(v5.0)	To align with CSP

	response evaluable analysis set and clarify the FAS definition is the same as the SAF. Also updated the list of outcomes and analysis sets to indicate ORR will use the response evaluable analysis set. Applies to Section 2.1 and Table 7		
10 Sep. 2020	Updated test on analysis methods to refer to the response evaluable analysis set where applicable. Applies to Section 4.1 4.3 and 4.3.1	Y(v5.0)	To align with CSP
10 Sep. 2020	Updated the text on DCO to align with CSP. Applies to Section 4	Y(v5.0)	To align with CSP
10 Sep. 2020	Updated the changes from the protocol section to indicate that there is an inconsistency in the CSP and the SAP. Applies to Section 6	NA	To improve previous intent
	Corrected definition of DLT-evaluable subjects to specify >65% of paclitaxel dose rather than >=65%. Applies to Section 3.3.3.1	NA	To improve previous intent
	Updated the definition of average dose intake to confirm that the average over all cycles has to be taken. Applies to Sections 3.3.4 and 8.3.6.2	NA	To improve previous intent
	Added a general rule for calculation of time windows for safety data. Applies to Section 3.6.2	NA	To improve previous intent
	Added Paclitaxel to the list of treatments for actual dose intake and RDI summaries. Applies to Section 3.3.4 and 4.4.3	NA	To align with regulatory request
01 Nov. 2021	Added new study arm (Arm 7), Durvalumab + Dato-DXd (datopotamab deruxtecan; DS-1062a)	Y (v6.0)	To align with CSP
04 Oct. 2023	Added the figures showing how the dosing interval is received for Arm 8. Applies to Section 8.1	Y (v10.0)	To improve previous intent
04 Oct. 2023	For Section 1.3; added explanation of arm 8, updated overview of study design figure, recruitment to arm 6 updated to be pathologically confirmed documentation, not just documented, added recruitment criteria arm 8, safety run in not needed	Y (v10.0)	To align with CSP
04 Oct. 2023	For Section 3.3.1, SAE updated to be collected from pre-screening ICF to main ICF	Y (v10.0)	To align with CSP

	04 Oct. 2023	For Section 3.5.4, added biomarker data to be used across different arms	Y (v10.0)	To align with CSP
	04 Oct. 2023	Updated Section 2.2 for version 3.0 of the PD Plan.	Y (v10.0)	To align with CSP
	10 Dec. 2024	Adverse Events of Special interest for Dato-DXd (Arm 7 and 8) aligned with the updated Dato-DXd IB.	Y (v11.0)	To align with CSP and Dato-DXd IB
Data presentation	22 Aug. 2019	Language used for QTcF calculation modified and derivation of RR added. Applies to Section 3.3.7	NA	To improve previous intent
	22 Aug. 2019	Further details added to the definition of baseline for efficacy variables. Applies to Section 3.6.1	NA	To improve previous intent
	22 Aug 2019	Summary of DoR (swimmer plot) added. Applies to Section 4.3.3	NA	To improve previous intent
	22 Aug. 2019	Summaries of exposure added. Applies to Section 4.4.3	NA	To improve previous intent
	22 Aug. 2019	Summaries of QTcF added. Applies to Sections 4.4.5	NA	To improve previous intent
	22 Aug. 2019	Removed all references to the selumetinib arm (Arm 3). Applies to Sections 1.2 and 3.3.4, Figure 1, Table 12 and Section 8.1	Y (v3.0)	Arm is no longer being considered for the study and has been removed from CSP
	22 Aug. 2019	Removed nicotine use from list of baseline characteristics. Applies to Section 3.5.1	NA	To improve previous intent
	22 Aug. 2019	Added that listings would be produced for arms that do not meet RP2D. Applies to Section 4.1	NA	To improve previous intent
	08 Oct. 2019	Modified derivation of average dose intake. Applies to Section 4.4.3	NA	To improve previous intent
	08 Oct. 2019	Removed arm 3 and updated footnotes. Applies to Table 12	Y (v3.0)	To align with CSP
	08 Oct. 2019	Modified the list of baseline characteristics. Applies to Section 3.5.1	NA	To improve previous intent
	08 Oct. 2019	Modified the subjects who will be used for the study drug administration listings. Applies to Section 4.2.5	NA	To improve previous intent
	08 Oct. 2019	Added text to say that dose delays, reductions and interruptions will be summarized. Applies to Section 4.4	NA	To improve previous intent
	08 Oct. 2019	Modified list of summaries of AEs. Applies to Section 4.4.1	NA	To improve previous intent
	08 Oct. 2019	Added text to clarify what happens when AEs have missing causality and removed text on completely missing AE stop dates. Applies to Section 3.6.3	NA	To improve previous intent

08 Oct. 2019	Removed “relevant” from surgical history in demographic/baseline characteristics. Applies to Section 4.2.3	NA	To improve previous intent
09 Oct. 2019	Modified text on immunogenicity analysis by correcting population used and adding “of maximum titer”. Applies to Section 4.6	NA	To improve previous intent
	Added text on ECGs to indicate what would be presented when an triplicate categorical evaluations are given for a visit. Applies to Section 4.4.5	NA	To improve previous intent
03 Sep. 2020	Removed reference to the 80% Clopper-Pearson CIs for ORR	Y(v5.0)	To align with CSP
	Added text on duration of follow-up and its summaries. Applies to Sections 3.2.7 and 4.3.6	NA	To improve previous intent
01 Nov. 2021	Added text to indicate what summaries may be produced to show the impact of the COVID-19 pandemic (section 4.4.9)	NA	To align with CSP
01 Nov. 2021	Updated ORR analysis for the arm proceeding to Part 2. Clopper-Pearson CIs updated to mid-p CIs	NA	To improve previous intent
04 Oct. 2023	In section 4, DCO for final analysis for arms 1/2/5/6 updated and arm 7/8 also	Y(v10.0)	To align with CSP
10 Dec. 2024	Adverse Events of Special interest for Dato-DXd (Arm 7 and 8) aligned with the updated Dato-DXd IB.	Y(v11.0)	To align with CSP and Dato-DXd IB

1 STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the clinical study protocol (CSP). This SAP is based on version 11 of the CSP.

This SAP will apply to the phase IB/II, 2-stage study to determine the efficacy and safety of durvalumab in combination with novel oncology therapies (i.e. capivasertib, oleclumab, DS-8201a [trastuzumab deruxtecan also referred to as T-DXd], and Dato-DXd [datopotamab deruxtecan]) with or without paclitaxel and durvalumab plus paclitaxel for first-line metastatic (Stage IV) triple negative breast cancer (TNBC). The study is designed to concurrently evaluate potential novel treatment combinations with clinical promise using a CCI test to evaluate which cohorts may proceed to expansion.

The target population for this study is adult female subjects (age ≥18 years) with metastatic (Stage IV) locally confirmed TNBC, as defined by the most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, and no prior exposure to treatment for metastatic (Stage IV) TNBC.

1.1 Study objectives – Part 1

1.1.1 Primary objective

The primary objective for Part 1 of this study and the corresponding endpoints/variables are shown in Table 1.

Table 1: Primary study objective and corresponding endpoints/variables

Objective	Endpoints/variables
To assess the safety and tolerability profile of durvalumab + novel oncology therapies with or without paclitaxel and durvalumab + paclitaxel	AEs, exposure, physical examinations, laboratory findings, ophthalmologic assessments (Arms 7 and 8 only), and vital signs

AEs Adverse events

1.1.2 Secondary objectives

The secondary objectives for Part 1 of this study and the corresponding endpoints/variables are shown in Table 2.

Table 2: Secondary study objectives and corresponding endpoints/variables

Objective	Endpoints/variables
To assess the efficacy of durvalumab + novel oncology therapies with or without paclitaxel and durvalumab + paclitaxel in terms of ORR, PFS, DoR, and OS	Endpoints based on investigator assessment of RECIST 1.1: • ORR: The percentage of evaluable subjects with a confirmed Investigator-assessed visit response of CR or PR

	• PFS: Time from date of first dose until the date of objective radiological disease progression using RECIST 1.1 or death (by any cause in the absence of progression) • DoR: Time from date of first detection of objective response (which is subsequently confirmed) until the date of objective radiological disease progression • OS: Time from date of first dose until the date of death by any cause
To assess the PK of durvalumab and novel oncology therapies (i.e. oleclumab, DS-8201a, and Dato-DXd) in all treatment arms	Serum concentration of durvalumab and serum or plasma concentration of novel oncology therapies
To investigate the immunogenicity of durvalumab and applicable novel oncology therapies (i.e. oleclumab, DS-8201a, and Dato-DXd) in all applicable treatment arms	Presence of ADAs for durvalumab and applicable novel oncology therapies

ADAs Anti-drug antibodies; CR Complete response; Dato-DXd Datopotamab deruxtecan; DoR Duration of response; ORR Objective response rate; OS Overall survival; PFS Progression free survival; PK Pharmacokinetics; PR Partial response; RECIST Response evaluation criteria in solid tumors

1.1.3 Exploratory objectives

The exploratory objectives for Part 1 of this study and the corresponding endpoints/variables are shown in Table 3. The exploratory analyses related to tumor size may be reported with the primary analysis clinical study report (CSR). All other exploratory analyses may be reported separately.

Table 3: Exploratory objectives and corresponding endpoints/variables

Objective	Endpoints/variables
To collect blood and tissue samples to evaluate molecular/biological responses and/or identify candidate markers that may correlate with the likelihood of clinical benefit	Blood and CCI [redacted], including but not limited to the following, and their association with treatment benefit: • CCI [redacted] detected by H&E • CCI [redacted] detected by IHC • CCI [redacted] • CCI [redacted]
To further assess the efficacy of durvalumab + novel oncology therapies with or without paclitaxel and durvalumab + paclitaxel in terms of change in tumor size	Change in tumor size

CCI [redacted]; H&E Hematoxylin and eosin stain; IHC Immunohistochemistry; CCI [redacted]

1.2 Study objectives – Part 2

All mentioned endpoints for Part 2 will be analyzed in the data set of Part 1 plus Part 2 subjects in each cohort and additionally may be analyzed for each part separately.

1.2.1 Primary objectives

The primary objective for Part 2 of this study and the corresponding endpoints/variables are shown in Table 4.

Table 4: Primary study objectives and corresponding endpoints/variables

Objective	Endpoints/variables
To assess the efficacy of durvalumab + novel oncology therapies with or without paclitaxel in terms of ORR	Endpoint based on Investigator assessment of RECIST 1.1: • ORR: The percentage of evaluable subjects with an Investigator-assessed visit response of CR or PR. Part 1 and Part 2 data will be pooled for efficacy analysis.

CR Complete response; ORR Objective response rate; PR Partial response; RECIST Response evaluation criteria in solid tumors

1.2.2 Secondary objectives

The secondary objectives for Part 2 of this study and the corresponding endpoints/variables are shown in Table 5.

Table 5: Secondary study objectives and corresponding endpoints/variables

Objective	Endpoints/variables
To further assess the efficacy of durvalumab + novel oncology therapies with or without paclitaxel and in terms of PFS, DoR, OS and PFS6[a]	Endpoints based on investigator assessment of RECIST 1.1: • PFS: Time from date of first dose until the date of objective radiological disease progression using RECIST 1.1 or death (by any cause in the absence of progression) • DoR: Time from date of first detection of objective response (which is subsequently confirmed) until the date of objective radiological disease progression • PFS6: PFS at 6 months following date of first dose • OS: Time from date of first dose until the date of death by any cause

To assess the safety and tolerability profile of durvalumab + novel oncology therapies with or without paclitaxel	AEs, exposure, physical examinations, laboratory findings, ophthalmologic assessments (Arms 7 and 8 only), and vital signs

[a] Progression-free survival at 6 months following date of first dose (PFS6) is equivalent to the proportion of subjects alive and progression free at 6 months following date of first dose (APF6).

AE Adverse event; DoR Duration of response; OS Overall survival; PFS Progression-free survival; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1;

1.2.3 Exploratory objectives

The exploratory objectives for Part 2 of this study and the corresponding endpoints/variables are shown in Table 6. All exploratory analyses may be reported separately.

Table 6: Exploratory objectives and corresponding endpoints/variables

Objective	Endpoints/variables
To collect blood and tissue samples to evaluate molecular/biological responses and/or identify candidate markers that may correlate with the likelihood of clinical benefit	Blood and CCI, including but not limited to the following, and their association with treatment benefit: • CCI detected by H&E • CCI detected by IHC • CCI • CCI

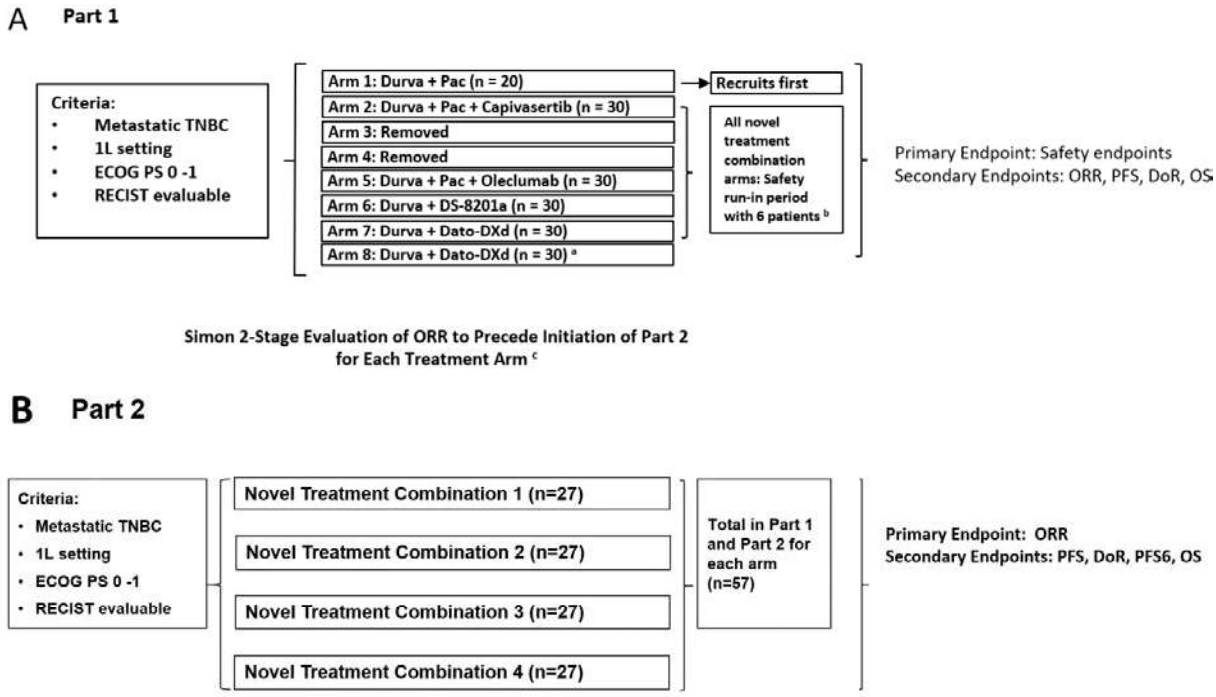
CCI; H&E Hematoxylin and eosin stain; IHC Immunohistochemistry; CCI

1.3 Study design

This is a Phase Ib/II, 2-stage, open-label, multicenter study to determine the efficacy and safety of durvalumab in combination with novel oncology therapies (i.e. capivasertib, oleclumab, DS-8201a [trastuzumab deruxtecan, also referred to as T-DXd], and Dato-DXd [datopotamab deruxtecan]), as described in Section 2.2 of the CSP) with or without paclitaxel and durvalumab and paclitaxel as first-line treatment in subjects with metastatic (Stage IV) TNBC. The efficacy and safety of durvalumab + Dato-DXd in subjects with programmed cell death ligand 1 (PD-L1) positive TNBC will also be evaluated in Arm 8 in order to further assess safety and efficacy in subjects with PD-L1 positive tumors. The study is designed to concurrently evaluate potential novel treatment combinations with clinical promise using a 2-stage approach (Part 1 and Part 2). There is a Phase Ib study (Part 1) to assess safety and initial efficacy and a Phase II study (Part 2) that will expand subject enrollment if an adequate efficacy signal is observed in Part 1, based on an efficacy/futility analysis of the response rate

as defined by the CCI [redacted]. An overview of the study design is shown in Figure 1 and the treatment arms are defined in Table 7.

Figure 1: Overview of study design



[a] In subjects with PD-L1 positive status.

[b] In Part 1, the novel treatment combination arms will include a safety run-in period with a planned enrollment of 6 subjects. Fewer than 6 subjects may be enrolled if 2 subjects have DLTs before 6 subjects are enrolled; more than 6 subjects may be enrolled in order to have 6 DLT-evaluable subjects who complete the safety run-in with no DLTs reported. No safety run-in will occur in Arm 8 given that the durvalumab + Dato-DXd combination was found to be tolerable with no DLTs in Arm 7.

[c] See Section 1.4 for more details.

1L First-line; DLT Dose-limiting toxicity; DoR Duration of response; Durva Durvalumab; ECOG Eastern Cooperative Oncology Group; ORR Objective response rate; OS Overall survival; Pac Paclitaxel; Dato-DXd Datopotamab deruxtecan; DS-8201a Trastuzumab deruxtecan; PFS Progression-free survival; PFS6 Progression-free survival 6 months following date of first dose; PS Performance status; RECIST Response Evaluation Criteria in Solid Tumors; TNBC Triple negative breast cancer.

Table 7: Treatment arms

Part	Treatment arm	Study treatments
1	1	durvalumab + paclitaxel
1	2	durvalumab + paclitaxel + capivasertib
1	5	durvalumab + paclitaxel + oleclumab
1	6	durvalumab + DS-8201a (trastuzumab deruxtecan)

1	7	durvalumab + Dato-DXd (datopotamab deruxtecan)
1	8	durvalumab + Dato-DXd (datopotamab deruxtecan) [a]
2		Treatment arms that meet pre-defined endpoints from Part 1 may be expanded in Part 2

[a] Subjects with PD-L1 positive status

Safety and tolerability

The safety and tolerability of each treatment combination will be assessed, with safety being the primary objective. The first 20 subjects will be enrolled to the durvalumab + paclitaxel treatment arm (Arm 1) and these subjects will be monitored for toxicity. Additional subjects may be enrolled so there are at least 20 evaluable (i.e. dosed) subjects in this treatment arm. Arm 1 will employ a standard durvalumab dosing regimen (1500mg every 4 weeks (q4w)) with paclitaxel (90mg/m^2 4-week cycles: 3 weeks once weekly (days 1, 8, 15 of each cycle), 1 week off).

Subject assignment to one of the novel treatment combination arms (Arms 2, 5, 6, 7, 8) that are open to enrollment will start after the completion of recruitment to Arm 1 (as per Section 6.2.1 of the CSP). Here, a Randomization and Trial Supply Management System (RTSM) (Interactive Response Technology; IRT) will centrally assign the eligible subject to one of the open treatment arms (i.e. for which the novel oncology therapy is available). One randomization list will be used for each country. For recruitment to Arm 6, subjects must provide pathologically-confirmed documentation of advanced/unresectable or metastatic breast cancer with HER2 low expression (see Section 5.1 and 5.2 of the CSP for Arm specific inclusion and exclusion criteria). For recruitment to Arm 8, subjects must provide pathologically-confirmed documentation of advanced/unresectable or metastatic TNBC with PD-L1 positive status, as determined by pre-existing test or by local testing during pre-screening.

Each novel treatment combination arm will undergo a run-in period, in which 6 subjects are planned to be enrolled to initially inform the safety profile and determine the recommended Phase II dose (RP2D). Safety run-in will not occur in Arm 8 as the treatment combination was already evaluated in Arm 7 and found to be tolerable with no DLTs reported. Fewer than 6 subjects may be enrolled if 2 subjects have dose-limiting toxicities (DLTs) before 6 subjects have been enrolled; more than 6 subjects may be enrolled so there are 6 DLT-evaluable subjects in each of the novel treatment combination arms. Here, a DLT-evaluable subject is a subject who has received the full prescribed dose of durvalumab and:

- Arms 2 through 5: >65% of the prescribed number of doses of paclitaxel and of the novel oncology therapy during Cycle 1 (Weeks 0 through 3), and either has completed the first 28-day cycle or has a DLT during the first 28-day cycle.

- Arms 6 and 7: received the prescribed dose of DS-8201a or Dato-DXd therapy, respectively, during Cycle 1 (Weeks 0 through 2), and either has completed the first 21-day cycle or has a DLT during the first 21-day cycle.

If a subject experiences a DLT that causes them to receive less than the prescribed number of doses stated above in their first cycle, then the subject will still be considered DLT-evaluable. Subjects who are not DLT-evaluable by this definition will be replaced.

A safety review committee (SRC) will review data from the study and will monitor safety data on an ongoing basis. The SRC will evaluate the safety and tolerability of each combination and may confirm the RP2D or recommend dose modification based on 6 DLT-evaluable subjects who have completed the first treatment cycle (28 days of dosing for Arms 2 through 5, 21 days of dosing for Arms 6 and 7) or had a DLT. Additional details are provided in the SRC Charter. In the event that recruitment is paused for all novel treatment arms concurrently while they undergo their DLT review period, subjects in screening will have the opportunity to be assigned to Arm 1 to avoid delay in receiving treatment.

A novel treatment combination dose will be considered non-tolerated if 2 or more of up to 6 DLT-evaluable subjects experience a DLT at the combination dose level. If the initial dose level of the novel oncology therapy is not tolerated, a new cohort with up to 6 new DLT-evaluable subjects will be opened at a lower dose level; this process may be repeated until the lowest dose level is reached. If the lowest dose is not tolerated, no additional subjects will be enrolled to evaluate that novel treatment combination.

If subjects in the safety run-in period tolerate a given novel treatment combination (i.e. less than 2 of 6 DLT-evaluable subjects experience DLTs after 28 (Arms 2 through 5) or 21 (Arms 6 and 7) days of dosing at a given dose level), the SRC will determine an RP2D and an additional 24 subjects will be enrolled so that a total of 30 subjects are enrolled at the RP2D. Additional subjects may be enrolled so there are 30 evaluable (i.e. dosed) subjects in the treatment arm.

Arms 2 and 5 will employ a standard durvalumab dosing regimen (1500mg every 4 weeks (q4w)) with paclitaxel (80 mg/m^2 for Arm 2, 90mg/m^2 for Arm 5 in 4-week cycles: 3 weeks once weekly (days 1, 8, 15 of each cycle), 1 week off). Arms 6 and 7 will employ a durvalumab dosing regimen of 1120mg every three weeks (q3w). Note: prior to CSP v4.0, Arm 2 employed a paclitaxel dosing regimen of 90 mg/m^2 every four weeks. Subjects recruited to the study under this regimen may continue unchanged, as clinically indicated. The dose levels used for the novel oncology therapies during the safety run in are summarized in Table 8. Further information on dosing and dose modifications can be found in Sections 6.1 and 6.5 of the CSP, respectively.

Table 8: Dose level modification in cohorts with dose reduction during the safety run-in period

		Dose Level		
Study agent	Treatment arm	Initial dose (level 1)	Dose level -1	Dose level -2
Capivasertib	2	400 mg bid oral 4 days on (D2, D3, D4, and D5) and 3 days off in 4-week cycles: 3 weeks on (intermittent; see above) and 1 week off	CCI	
Oleclumab	5	3000 mg IV q2w first 2 cycles, then q4w starting at C3 (D1)		
DS 8201a (trastuzumab deruxtecan)	6	5.4 mg/kg IV q3w		
Dato-DXd (datopotamab deruxtecan)	7 and 8	6.0 mg/kg IV q3w		

bid Twice daily; C Cycle; D day, IV Intravenous; q1w Every 1 week; q2w Every 2 weeks; q3w Every 3 weeks; q4w Every 4 weeks

Efficacy

Efficacy will be evaluated as a secondary endpoint with objective response rate (ORR) as the key secondary endpoint. Part 1 of the study uses a CCI rule of 17 out of 30 (unconfirmed) responses. The final analysis uses the ORR (of confirmed responses) for 30 subjects, or if there is an extension to Part 2, of 57 subjects. Assessments based on confirmed ORR, as determined by the Investigator according to RECIST 1.1 as described in section 3.2.1, will be made when each novel treatment cohort has completed enrollment (i.e. 30 evaluable subjects) and all subjects have either had the opportunity to complete at least two on-treatment response evaluation assessments or have discontinued treatment. Each cohort is independent, and any signal observed in one arm will not have an impact on other arms.

1.4 Number of subjects

This study will enroll at least 20 (durvalumab + paclitaxel arm) or 30 (novel treatment arms) evaluable (i.e. dosed) subjects per treatment arm. This is considered appropriate to characterize the adverse event (AE) profile of each treatment combination. Part 2 of the study may enroll a further 27 subjects in each treatment arm that meets the CCI criteria.

The study is sized to allow the use of a CCI for each treatment arm according to the targeted ORR improvement from CCI CCI Each treatment arm (with the exception of Arm 1) requires CCI response-evaluable subjects (CCI in Part 1 and CCI in Part 2). If at least CCI out of CCI subjects achieve a response, then the treatment arm may continue to Part 2; otherwise further recruitment to this treatment arm will be stopped. If there are at least CCI out of CCI evaluable subjects achieving a response

in a treatment arm, then the data for that cohort will be considered as having an adequate efficacy signal.

2 ANALYSIS SETS

2.1.1 Definition of analysis sets

There are four analysis sets defined in this study. A summary of the analysis sets used for each outcome variable is provided in Table 9.

Table 9: Summary of outcome variables and analysis populations

Outcome variable	Populations
Demographics and baseline characteristics	Full analysis set
Efficacy data: DoR, PFS, change in tumor size[b], OS	Full analysis set
Efficacy data: ORR	Response evaluable analysis set
Safety data: Exposure[a], AEs (including SAEs), laboratory measurements, physical examinations, vital signs, and ADA	Safety analysis set
PK data[b]	PK analysis set
CCI [redacted]	Full analysis set

a This includes durvalumab, paclitaxel, capivasertib, oleclumab, DS-8201a, and Dato-DXd dose delays, reductions, and discontinuations.

b Change in tumor size and PK data are applicable for Part 1 only.

ADA Anti-drug antibody; AE Adverse event; AESI Adverse event of special interest; DLT Dose limiting toxicity; Dato-DXd Datopotamab deruxtecan; DS-8201a Trastuzumab deruxtecan; DoR Duration of response; ORR Objective response rate; OS Overall survival; PFS Progression-free survival; PK Pharmacokinetics

2.1.2 Full analysis set

The full analysis set (FAS) includes all subjects assigned to treatment who received any amount of study treatment (at least 1 investigational product (IP) [durvalumab, paclitaxel, or novel oncology therapy]). The FAS will be used for all efficacy and exploratory analyses. Treatment arms will be summarized according to treatment received. If a subject receives more than one novel oncology therapy in error, they will be summarized according to the first valid combination as listed in Table 7. The oncology therapy received in error will not be considered as part of the valid treatment combination. This is the same as for the safety analysis set.

2.1.3 Response evaluable analysis set

The response evaluable analysis set includes all subjects in the FAS who have measurable disease at baseline. This will be the primary analysis set on which ORR analyses will be performed. Further detail for this analysis set for ORR is included in Section 3.2.1.

2.1.4 Safety analysis set

The safety analysis set (SAF) includes all subjects who received any amount of study treatment (at least 1 investigational product (IP) [durvalumab, paclitaxel, or novel oncology therapy]). Safety data will not be formally analyzed but summarized using the SAF according to the treatment actually received. If a subject receives any amount of an experimental therapy, they will be summarized in the treatment arm corresponding to the first experimental treatment they received. If a subject only receives therapy from the durvalumab arm, they will be summarized in the durvalumab treatment Arm 1. If a subject receives more than one novel oncology therapy in error, they will be summarized according to the first valid combination as listed in Table 7. The oncology therapy received in error will not be considered as part of the valid treatment combination.

Subjects in the SAF with a non-missing baseline anti-drug antibody (ADA) result for an agent and at least one non-missing post-baseline ADA result for the same agent will form a subset of the SAF, the ADA-evaluable set. For example, ADA analyses for durvalumab will require subjects in the SAF who have a non-missing baseline durvalumab ADA result and at least one non-missing post-baseline durvalumab ADA result. All ADA analyses will be based on the ADA-evaluable set.

2.1.5 Pharmacokinetics analysis set

The PK analysis set includes all subjects who received at least 1 dose of durvalumab or novel oncology therapy per protocol for whom any post-dose evaluable PK data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the AstraZeneca Clinical Pharmacologist and Statistician prior to any analyses being performed. The PK analysis set will be summarized according to the treatment actually received. Note: the post-dose PK data must be on the same agent.

2.2 Violations and deviations

Protocol deviations will be collected, reviewed and reconciled throughout the study. Important protocol deviations (IPDs) will be identified from the complete set of protocol deviations. IPDs are those which may significantly impact the reliability of the study data or that may significantly affect a subjects's rights, safety, or wellbeing.

A set of pre-determined IPDs are listed in the Protocol Deviations Plan. The protocol deviations plan also indicates which IPDs will be identified by programmatic checks.

The IPDs are grouped in to the following IPD categories and will be programmatically derived from CCI [redacted] data or via manual validation checks. These will be listed

and summarized by randomized treatment group and discussed in the CSR as appropriate. Refer to the CSP for full details of the inclusion/exclusion criteria.

For this study, the following six general categories will be identified within the clinical database. These will be listed and discussed in the CSR as appropriate:

- Subjects who deviate from inclusion/exclusion criteria per the CSP

  Inclusion criteria deviations

  - Inclusion 1: Capable of giving signed informed consent
  - Inclusion 2: Written informed consent form (ICF) not obtained prior to performing any protocol related procedures
  - Inclusion 3: Written CCI not obtained prior to collection of optional samples
  - Inclusion 5: Locally confirmed advanced/unresectable or metastatic TNBC, determined from the most recent tumor sample taken for diagnostic purposes
  - Inclusion 6: No prior treatment for metastatic (Stage IV) TNBC or locally advanced unresectable TNBC. Prior treatment with curative intent for Stage I to III TNBC (that subsequently became metastatic) is acceptable if it meets the following criteria at the time of screening:
    - ≥6 months elapsed between the completion of treatment (eg, date of primary breast tumor surgery or the date of the last adjuvant chemotherapy administration, whichever occurred last) and the first documented distant disease recurrence
    - ≥12 months since the last administration of taxane
  - Inclusion 9: At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline. Tumor assessment by CT scan or MRI must be performed within 28 days prior to treatment assignment/randomization.
  - Inclusion 10: Adequate organ and marrow function as defined in protocol

  Additional criteria for subjects enrolled in Arm 6 (durvalumab + DS-8201a):

- Inclusion 14: Must provide documentation of locally determined advanced/unresectable or metastatic TNBC with HER2-low tumor expression (IHC 2+/ISH–, IHC 1+/ISH–, or IHC 1+/ISH untested)

Additional criteria for subjects enrolled in Arm 8 (Dato-DXd):

- Inclusion 18: PD-L1 positive tumor as determined by an IHC based assay. Pre-existing test results are acceptable. Where no result exists a positive local test result must be obtained during prescreening.

Exclusion criteria deviations

- Exclusion 2: Active or prior documented autoimmune or inflammatory disorders (see CSP for exceptions)
- Exclusion 11: Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG[redacted]
- Exclusion 12 (for Arm 2 subjects only): Any factors that increase the risk of QTc prolongation or risk of arrhythmic events as defined in the CSP
- Exclusion 13: Experience of any of the following procedures or conditions in the preceding 6 months: [redacted]
- Exclusion 14: Known allergy or hypersensitivity to any of the study treatment or any of the study treatment excipients
- Exclusion 15 (for Arm 5 subjects only): History of venous thromboembolism within the past 3 months
- Exclusion 16: Any concurrently chemotherapy, study treatment, biologic or hormonal therapy for cancer treatment (see CSP for exceptions)
- Exclusion 17: Prior exposure to immune-mediated therapy, including but not limited to, other anti-CTLA-4, [redacted] anti-PD-L1, or anti-PD-L2 antibodies, [redacted]
- Exclusion 19: Receipt of live attenuated vaccine within [redacted] days prior to the first dose of study treatment as defined in the protocol

- Exclusion 21: Current or prior use of immunosuppressive medication within CCI days before the first dose of IP (see protocol for exceptions to this)
- Exclusion 23 (for Arm 2 subjects only): Potent inhibitors or inducers or substrates of CYP3A4 or substrates of CYP2D6 within 2 weeks before the first dose of study treatment (3 weeks for St John's Wort)
- Exclusion 26: Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
- Exclusion 31 (for Arm 2 subjects only): Clinically significant abnormalities of glucose metabolism (see protocol for details)
- Exclusion 34: Cardiac ejection fraction outside institutional range of normal or <50% (whichever is higher) as measured by echocardiogram (or multiple-gated acquisition [MUGA] scan if an echocardiogram cannot be performed or is inconclusive)
- Exclusion 36 (for Arm 6, Arm 7, and Arm 8 subjects only): History of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
- Exclusion 37 (for Arm 6, Arm 7, and Arm 8 subjects only): CCI [redacted]
- Exclusion 41 (for Arm 6, Arm 7, and Arm 8 subjects only): Use of chloroquine or hydroxychloroquine in <14 days prior to Day 1 of DS-8201a or Dato-DXd treatment
- Exclusion 44 (for Arm 6 subjects only): Previously been diagnosed as HER2-positive breast cancer or received HER2-targeted therapy
- Exclusion 35 (for Arm 7 and Arm 8 subjects only): Clinically significant corneal disease in the opinion of the Investigator

  - Exclusion 39 (for Arm 7 and Arm 8 subjects only): Received radiation therapy including palliative stereotactic radiation therapy to chest ≤4 weeks of enrollment or palliative stereotactic radiation therapy to other areas ≤2 weeks of enrollment

- Discontinuation Criteria for study product met but subject not withdrawn from study treatment
  - Withdrawal of consent from further treatment with IP
  - An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
  - Any AE that meets the criteria for discontinuation as defined in the dosing modification and toxicity management guidelines for durvalumab or any novel oncology therapy (see CSP for exceptions to this) or as defined in the local prescribing information for paclitaxel
  - Clinical progression or RECIST 1.1-defined radiological progression and Investigator determination that the subject is no longer benefiting from treatment with IP
  - Pregnancy or intent to become pregnant
  - Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
  - Initiation of alternative anticancer therapy including another investigational agent

- IP deviation
  - Subject received incorrect IP
  - Subject received incorrect dose of IP [redacted]
  - Use of expired IP
  - Subject with a known allergy or hypersensitivity

- Excluded Medications taken

- Subject received concomitant medication defined as prohibited in the CSP – see CSP for exceptions to this

- Deviations to study procedure
  - RECIST scans not performed at all on 2 successive occasions.
  - (For Arm 6 only) No chest high-resolution computed tomography (CT) scan nor CT scan performed at screening.

- Other IPDs
  - Missing PI eCRF signature at DBL

Subjects who receive the wrong treatment at any time will be included in the safety analysis set as described in Section 2.1.1. During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the study team leader and/or statistician.

None of the deviations will lead to subjects being excluded from the analysis sets described in Section 2.1.1. (with the exception of the PK analysis set, if the deviation is considered to impact upon PK).

2.3 Monitoring of important protocol deviations

The IPDs will be programmatically identified within the clinical database by programmed edit checks or via manual validation checks. A programmatically derived IPD report will be created listing all identified IPDs and the data used to identify them. This report will be reviewed at regular IPD review meetings held on at least a quarterly basis. At this meeting, programmatically derived IPDs will be checked to ensure they have been correctly classified.

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

The final classification of IPDs will be made prior to database lock.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Derivation of RECIST visit responses

For all subjects, the RECIST tumor response data will be used to determine each subject's visit response according to RECIST version 1.1 (Appendix F of the CSP). It will also be used to evaluate for progression of disease. Tumor assessments by the Investigator will be

performed on images from CT [preferred] or magnetic resonance imaging (MRI), each with IV contrast, of the chest and abdomen (including the entire liver and both adrenals). Additional anatomy (eg. pelvis) should be imaged based on signs and symptoms of individual subjects at baseline and follow-up. Subjects with suspected brain metastases at screening should have an MRI (preferred) or CT, each with IV contrast, of the brain prior to study entry. Brain metastases will not be recorded as RECIST target lesions (TL) at baseline.

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including the entire liver and both adrenal glands) must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the subject, e.g. new lesions at follow-up.

Baseline radiological tumor assessments are to be performed no more than 28 days before the date of treatment assignment and ideally should be performed as close as possible to the date of treatment assignment. Post-baseline tumor assessments by the Investigator will be performed at the following time points:

- Every 8 weeks (± 1 week) until 48 weeks relative to the date of treatment assignment, and every 12 weeks (± 1 week) thereafter until radiological progression (Arms 1 through 5).

- Every 6 weeks (± 1 week) until 48 weeks relative to the date of treatment assignment, and every 12 weeks (± 1 week) thereafter until radiological progression (Arms 6 through 8).

If an unscheduled assessment is performed, and the subject has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some subjects being assessed at a different frequency than other subjects. All confirmatory scans should be recorded in the database.

3.1.1 Site investigator assessment using RECIST 1.1

At each visit, subjects will be programmatically assigned a RECIST 1.1 visit response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) using the information from TLs, NTLs and new lesions and depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to treatment assignment. If a subject has had a tumor assessment that cannot be evaluated, then the subject will be assigned a visit response of not evaluable (NE), unless there is evidence of progression in which case the response will be assigned as PD.

3.1.1.1 Target lesions (TLs)

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

At baseline, a maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved and suitable for accurate repeated measurement will be identified as TLs at baseline. Lymph nodes, in any location, will be collectively considered a single organ with a maximum of two lymph nodes as TLs. If more than one baseline scan is recorded, then measurements from the one that is closest and prior to treatment assignment will be used to define the baseline sum of TLs. All other lesions (or sites of disease) not recorded as TL will be identified as NTL at baseline. Measurements are not required for these lesions, but their status will be followed at subsequent visits.

Measurable disease (i.e. at least one TL) is one of the entry criteria for the study. However, if a subject with non-measurable disease (i.e. no TLs) is enrolled in the study, the evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see Sections 3.1.1.2 and 3.1.1.3 for further details). If a subject does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

Table 10: Target lesion visit responses

Visit responses	Description
Complete response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10mm
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on 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 5mm
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not evaluable (NE)	Only relevant in certain conditions (i.e. if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit*; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

Not applicable (NA)	No target lesions recorded at baseline

*If an intervention was recorded for a target lesion at a previous visit, all subsequent visits should have intervention recorded for that target lesion

Rounding of TL data
For calculation of PD and PR for TLs percentage changes from baseline and nadir (previous minimum) should be rounded to one decimal place before assigning a TL response. For example, 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

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

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

Note: the nadir (i.e. smallest measurement) can only be taken from assessments where all the TLs had a longest diameter recorded.

If all TL measurements are missing, then the TL visit response is NE. If the sum of available TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥5mm, from nadir even assuming the non-recorded TLs have disappeared, the TL visit response is PD. Note: the nadir can only be taken from assessments where all the TLs had a LD recorded.

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

Lymph nodes
For lymph nodes, if the size (measured as the short axis diameter) reduces to < 10mm then these are considered non-pathological. However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10mm and all other TLs are 0mm then although the sum may be > 0mm the calculation of TL response should be over-written as a CR.

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

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met i.e. if a lymph node LD increases by 20% but remains < 10mm

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD is also met

- Step 3: If not all lesions meet the CR criteria (i.e. a pathological lymph node selected as TL has short axis >10mm and an absolute increase of ≥ 5mm taking as reference the smallest short axis for the same TL since treatment started including the baseline or the reappearance of previously disappeared lesion) or a new lesion appears, then response will be set to PD

- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR

TL too big to measure
If a TL becomes too big to measure this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team in the absence of as much information as possible regarding the subject's study arm. It is expected that a visit response of PD will remain in the clear majority of cases.

TL too small to measure
If a TL becomes too small to measure, a value of 5mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered that a smaller value can be reliably measured. If a TL response of PD results (at a subsequent visit), then this will be reviewed by the study team in absence of as much information as possible regarding the subject's study arm.

Irradiated lesions/lesion intervention
Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization), should be handled in the following way and once a lesion has had intervention, then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumors:

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

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

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

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

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

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

Table 11: Example of scaling

Lesion	Longest diameter (mm) at nadir visit	Longest diameter (mm) at follow-up visit
1	16	18
2	14	16
3	14	16
4	18	18

5	12	Intervention
Sum	**74**	**68**

Lesion 5 has had an intervention at the follow-up visit. It had a baseline measure of 74mm. The sum of lesions 1 – 4 at the follow-up is 68mm. The sum of the corresponding lesions at nadir visit is 62mm. Scale up as follows to give an estimated follow-up visit TL sum of 81mm:

$$\frac{68}{62} \times 74 = 81mm$$

Lesions that split in two or more parts
If a TL splits in two or more parts, then the longest diameters of the split lesions should be summed and reported as the longest diameter for the lesion that split.

Lesions that merge
If two or more TLs merge, then the longest diameter of the merged lesion should be recorded for one of the TL sizes and the other TL sizes should be recorded as 0mm.

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

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing. The TL visit response may still be evaluable if the number of missing TL measurements at a visit is ≤1/3 of the total number of TLs.

3.1.1.2 Non-target lesions and new lesions

At each visit, an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record the overall response for NTL at the investigational site at each visit.

NTL response will be derived based on the investigator's overall assessment of NTLs as follows:

Table 12: Non-target lesion visit responses

Visit responses	Description

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

NTL Non-target lesion; TL Target lesion

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

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

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

If a TL has completely disappeared and a lesion appears in the same location on a subsequent scan, it will be recorded as a new lesion.

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

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously new lesion has been assessed as unequivocal, and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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

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

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

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

3.1.1.3 Overall visit response

Table 13 defines how the previously defined TL and NTL visit responses will be combined with the new lesion information to give an overall visit response.

Table 13: Overall visit responses

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	None recorded	CR
CR	NA	None recorded	CR
CR	Non-CR/Non-PD	None recorded	PR
CR	NE	None recorded	PR
PR	Non-PD or NE or NA	None recorded	PR
SD	Non-PD or NE or NA	None recorded	SD
NE	Non-PD or NE or NA	None recorded	NE
PD	Any	Any (i.e. Yes / None recorded)	PD
Any	PD	Any (i.e. Yes / None recorded)	PD

Any	Any	Yes	PD
NA	CR	None recorded	CR
NA	Non-CR/Non-PD	None recorded	SD
NA	NE	None recorded	NE
NA	NA	None recorded	NE

CR Complete response; NA Not applicable; NE Not evaluable; PD Progressive disease; PR Partial response; SD Stable disease

3.2 Efficacy variables

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculation of efficacy variables. Unless otherwise stated for that parameter/analysis, this is also regardless of whether a subject discontinues study treatment or receives another anti-cancer therapy.

3.2.1 Objective response rate

The ORR is defined as follows:

- The number (%) of subjects with at least 1 visit response of CR or PR (confirmed by a follow-up scan at least 4 weeks later showing CR or PR)

ORR will be calculated using all subjects in the response evaluable analysis set who have measurable disease at baseline and have had the opportunity to complete least two on-treatment disease assessments (i.e. confirmed response) prior to progression, death, start of subsequent anti-cancer therapy and discontinuation of study treatment. Subjects with progression or who die will be included in ORR calculation, regardless of whether they completed two on-treatment disease assessments or not. The response evaluable analysis set will be used as the denominator for the efficacy evaluation of both Part 1 and the final analysis of ORR. To align the protocol definition with the different assessment conditions per Arm and possible immature data, subjects are included if they had the opportunity for two assessments, progressed, died or discontinued. The assessment period for Period 1 differs by Arm, and thus the time required for two on-treatment disease assessments will differ as per Table 14.

Table 14: Time for two on treatment assessments

Arm	Assessment period	Time for at least two on-treatment assessments plus 2 x 1 weeks for a late visit
1, 2 and 5	56 days (8 weeks)	126 days (18 weeks)
6, 7 and 8	42 days (6 weeks)	98 days (14 weeks)

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging, preferable at the next regularly scheduled imaging visit, and not less than four weeks after the visit when the response was first observed, with no evidence of progression between the initial and CR/PR confirmation visit. Both visits contributing to the confirmed response must be prior to any subsequent anti-cancer therapy or discontinuation of study treatment without progression, for the subject to be considered as a responder. Radiotherapy is not considered a subsequent anti-cancer therapy for this analysis. The final analysis of ORR will use confirmed response as the numerator. Unconfirmed response (i.e. a response recorded at a single assessment) will be used as the numerator in the analysis of ORR in Part 1, and as a sensitivity analysis in Part 2.

Data obtained up until the earliest of progression, death, start of subsequent anti-cancer therapy or discontinuation of study treatment without progression, will be included in the assessment of ORR. Responses that occur after progression, the start of subsequent anti-cancer therapy or after the subject goes off treatment without progression, will be excluded from the derivation of ORR.

3.2.2 Progression free survival

Progression-free survival (PFS) is defined as the time from the date of first dose of IP (at least 1 IP [durvalumab, paclitaxel, or novel oncology therapy]) until the date of objective PD or death (by any cause in the absence of progression) regardless of whether the subject discontinues from therapy or receives another anti-cancer therapy prior to progression (i.e. date of event or censoring – date of first dose+1). For Part 2, PFS at 6 months following date of first dose will also be calculated.

Subjects 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 1.1 assessment. However, if the subject progresses or dies immediately after 2 or more consecutive missed visits, the subject will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits (Note: NE visit is not considered as missed visit).

Given the scheduled visit assessment scheme for Arms 1 through 5 (i.e. eight-weekly from the date of treatment assignment for the first 48 weeks then 12-weekly thereafter) the definition of two missed visits will be as follows:

- If the previous RECIST assessment is <= day 49 (i.e. week 7) then two missing visits will equate to 17 weeks since the previous RECIST assessment, allowing for a late visit (i.e. 2 x 8 weeks + 1 week for a late assessment = 17 weeks)

- If the previous RECIST assessment is > day 49 and <= day 273 (i.e. week 39) then two missing visits will equate to 18 weeks since the previous RECIST assessment,

allowing for early and late visits (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks)

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

- From week 47 (day 330) onwards (when the scheduling changes to 12-weekly assessments, two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks)

Given the scheduled visit assessment scheme for Arms 6 through 8 (i.e. six-weekly from the date of treatment assignment for the first 48 weeks then 12-weekly thereafter) the definition of two missed visits will be as follows:

- If the previous RECIST assessment is <= day 35 (i.e. week 5) then two missing visits will equate to 13 weeks since the previous RECIST assessment, allowing for a late visit (i.e. 2 x 6 weeks + 1 week for a late assessment = 13 weeks)

- If the previous RECIST assessment is > day 35 and <= day 287 (i.e. week 41) then two missing visits will equate to 14 weeks since the previous RECIST assessment, allowing for early and late visits (i.e. 2 x 6 weeks + 1 week for an early assessment + 1 week for a late assessment = 14 weeks)

- If the two missed visits occur over the period when the scheduled frequency of RECIST assessments changes from 6-weekly to 12-weekly, this will equate to 20 weeks (i.e. take the average of 6 and 12 weeks which gives 9 weeks and then apply the same rationale, hence 2 x 9 weeks + 1 week for an early assessment + 1 week for a late assessment). The time period for the previous RECIST assessment will be from days 288 to 329 (i.e. week 41 to week 47)

- From week 47 (day 330) onwards (when the scheduling changes to 12-weekly assessments, two missing visits will equate to 26 weeks (i.e. 2 x 12 weeks + 1 week for an early assessment + 1 week for a late assessment = 26 weeks)

If a subject has no evaluable post-baseline visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline, then they will be treated as an event with date of death as the event date.

The PFS time will always be derived based on scan/assessment dates and not visit dates. RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- The date of progression will be determined based on the earliest of the RECIST 1.1 assessment/scan dates of the component that indicates progression
- When censoring a subject for PFS, the subject will be censored at the latest of the scan dates contributing to a particular overall visit assessment

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

3.2.3 Duration of response

For subjects who are classified as responders, the duration of (first documented) response (DoR) is defined as the time from the date of PFS event or censoring – date of first response +1 where:

- The date of first response is the latest of the dates contributing toward the first response of CR or PR that was subsequently confirmed
- The time of the end of response should coincide with the date of PD or death from any cause used for the PFS endpoint (see Section 3.2.1). If a subject does not progress following a response, then their DoR will be censored at the PFS censoring time. PFS will not be censored at date of subsequent therapy

3.2.4 Best objective response (BoR)

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST 1.1 assessment, described in Section 3.1. It is the best response a subject has had following treatment assignment up until the earliest date of progression, death, start of subsequent anti-cancer therapy or discontinuation of study treatment without progression.

Categorization of BoR will be based on RECIST 1.1 using the following response categories: CR, PR, SD, PD, and NE. CR or PR must be confirmed. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. In order to have SD as BoR, SD should be recorded at least 8 weeks minus 1 week (Arms 1 through 5) or 6 weeks minus 1 week (Arms 6 through 8) (to allow for an early assessment within the assessment window), after treatment assignment. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For subjects who die with no evaluable RECIST 1.1 assessments, if the death occurs <= 9 (Arms 1 through 5) or 7 (Arms 6 through 8) weeks (i.e. 8 weeks (or 6 weeks) + 1 week to allow for a late assessment within the assessment window), after treatment assignment, then BoR will be assigned to the progression (PD) category. For subjects who die with no evaluable RECIST 1.1 assessments, if death occurs > 9 (Arms 1 through 5) or 7 (Arms 6 through 8) weeks after treatment assignment then BoR will be assigned to the NE category.

The denominator for BoR will be consistent with those used in the ORR analysis. A subject will be classified as a responder if the RECIST 1.1 criteria for a CR or PR (confirmed response) are satisfied at any time following treatment assignment, prior to RECIST progression, death, start of subsequent anti-cancer therapy or discontinuation of study treatment without progression.

3.2.5 Overall survival

Overall survival (OS) is defined as the time from the date of first dose of IP (at least 1 IP [durvalumab, paclitaxel, or novel oncology therapy]) until death due to any cause regardless of whether the subject withdraws from therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of first dose +1). Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive (SUR_DAT, recorded within the SURVIVE module of the eCRF). For analyses where a survival sweep is performed, the SURVIVE module must be updated for every subject not known to have already died.

Note: Survival calls will be made following the date of a data cut-off (DCO) for the analysis (these contacts should generally occur within 7 days of the DCO). If subjects are confirmed to be alive or if the death date is post the DCO date, these subjects will be censored at the date of DCO. Death dates may be found by checking publicly available death registries. In a situation where a subject has actively withdrawn consent for the processing of their personal data, the survival status of the subject can be obtained by site personnel by checking publicly available resources (as applicable under local laws).

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

- AE start and stop dates
- Admission and discharge dates of hospitalization
- Study treatment date

- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on RECIST CRF
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF
- End of study date

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

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

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e. censored at the last known alive date.

3.2.6 Change in tumor size

The best percentage change from pre-dose in tumor size is the largest decrease from baseline (or smallest increase from baseline in the absence of reduction) for a subject using RECIST 1.1 assessments. All measurements up until the earliest of death in the absence of progression, any evidence of disease progression, the start of subsequent anti-cancer therapy or the last evaluable assessment (if the subject has not died, progressed or started subsequent anti-cancer therapy) will be included in this evaluation. The percentage change in tumor size at a specific visit may also be presented. The change in target lesion tumor size at week X will be obtained for each subject by taking the difference between the sum of the target lesions at week X and the sum of the target lesions at baseline. To obtain the percentage change in target lesion tumor size at week X the change in target lesion tumor size is divided by the sum of the target lesions at baseline and multiplied by 100 (i.e. (week X – baseline) / baseline * 100).

If the best percentage change cannot be calculated due to missing data (including if the subject has no TLs at baseline), a value of +20% will be imputed as the best percentage change from baseline in the following situations (otherwise best percentage change will be left as missing):

- If a subject has no post-baseline assessment and has died
- If a subject has new lesions or progression of NTLs or TLs
- If a subject has withdrawn due to PD and has no evaluable TL data before or at a PD

3.2.7 Duration of follow-up

The duration of follow-up will be calculated for subjects in the FAS. For those who have not died, this will be defined as date of OS censoring – treatment start date +1. For subjects who have died this will be defined as date of death – treatment start date +1.

3.3 Safety variables

Safety is the primary outcome for this study. Safety and tolerability will be assessed in terms of AEs (including serious adverse events [SAEs]), deaths, laboratory measurements, vital signs, ECG, Echocardiograms/multiple gated acquisition (ECHO/MUGA) scan and physical examinations, which will be collected for all subjects.

Data from all cycles of treatment will be combined in the presentation of safety data. The SAF will be used for reporting of safety data.

3.3.1 Adverse events

An adverse event is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. 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 treatment has been administered.

For this study, only SAEs will be collected from the time of the subject signing the pre-screening ICF until the main ICF is signed. Data on AEs and SAEs will be collected between the date of the subject signing the main ICF and 90 days following discontinuation of IP (i.e. the last dose of durvalumab + paclitaxel combination therapy, durvalumab + paclitaxel + novel oncology therapy combinations, durvalumab + DS-8201a or durvalumab + Dato-DXd). If an event starts outside of this period and it is considered possible that it is due to late onset toxicity to study drug, then it should be reported as an AE or SAE.

Treatment-emergent AEs [TEAEs] will be defined as any AEs that started after dosing or that started prior to dosing and worsened (by investigator report of a change in intensity) following exposure to treatment, up to 90 days following discontinuation of IP or start of subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first). If an AE is not worse than the baseline (pre-dose) severity, then it will not be classified as TEAE.

The Medical dictionary for regulatory activities (MedDRA) dictionary (latest or current version) will be used to code AEs. AEs will be graded according to the National Cancer Institute (NCI) common terminology criteria for adverse event (CTCAE) v4.03. The CTCAE grade will be assigned by the investigator as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

Missing start and stop dates for AEs will be handled using the rules described in Section 3.6.3.

3.3.2 Adverse events of special interest and adverse events of possible interest

Some clinical concepts (including some selected individual preferred terms and higher level terms) have been considered “AEs of special interest” (AESI) and “AEs of possible interest” (AEPIs) to the durvalumab program. All AESIs are being closely monitored in clinical studies using durvalumab alone, and durvalumab in combination with other anti-cancer agents.

3.3.2.1 Durvalumab

AESIs for durvalumab are defined as AEs with a likely inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab and requiring more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (for example, therapies for hyperthyroidism include beta blockers [e.g., propranolol], calcium channel blockers [e.g., verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate). In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions are also considered AESIs.

AEPIs are defined as AEs that could have a potential inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab but are more likely to have occurred due to other pathophysiological mechanisms, thus, the likelihood of the event being inflammatory or immune-mediated in nature is not high and/or is most often or usually explained by the other causes. These AEs not routinely arising from an inflammatory or immune-mediated mechanism of action – typically quite general clinical terms that usually present from a multitude of other causes –are classified as AEPIs.

These AESIs and AEPIs have been identified as Pneumonitis, Hepatic events, Diarrhea/Colitis, Intestinal perforations, Adrenal Insufficiency, Type 1 diabetes mellitus, Hyperthyroid events, Hypophysitis, Hypothyroid events, Thyroiditis, Renal events, Dermatitis/Rash, Pancreatic events, Myocarditis, Myasthenia gravis, Guillain-Barre syndrome, Myositis, Infusion/hypersensitivity reactions and Other rare/miscellaneous. Other categories may be added or existing terms may be merged as necessary. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which MedDRA preferred terms contribute to each AESI/AEPI. A further review will take place prior to Database lock (DBL) to ensure any further terms not already included are captured within the categories.

3.3.2.2 Capivasertib

For Capivasertib, AESIs have been identified as hyperglycemia, rash, diarrhea, stomatitis, infection/lower respiratory tract infection, and QT prolongation.

3.3.2.3 Oleclumab

For Oleclumab, AESIs have been identified as infusion related reactions, hypersensitivity (including anaphylactic reaction), cardiac chest pain, transient ischemic attack, thromboembolism, edema, and immune complex disease.

3.3.2.4 DS-8201a (trastuzumab deruxtecan)

Based on the available data, literature and reported toxicities for the same class of agents, AESI for DS-8201a have been identified as interstitial lung disease/pneumonitis, and left ventricular ejection fraction (LVEF) decrease.

3.3.2.5 Dato-DXd (datopotamab deruxtecan; DS-1062a)

Based on the available data, literature and reported toxicities for drugs with similar monoclonal antibody and payload, AESI for Dato-DXd have been identified as interstitial lung disease/pneumonitis, , oral mucositis/stomatitis, mucosal inflammation other than oral mucositis/stomatitis and ocular surface events.

3.3.3 Dose-limiting toxicity

3.3.3.1 DLTs

A DLT will be defined as the occurrence of a CCI (listed below) that is at least possibly related to durvalumab and/or the novel oncology therapy. AEs will be graded according to the NCI CTCAE version 4.03. The DLT observation window will run from the time of first dose until completion of the first cycle (28 days for Arms 2 through 5, 21 days for Arm 6 and Arm 7).

- CCI

- Any CCI , excluding the following:
  - CCI of any duration, unless associated with CCI
  - CCI or CCI lasting less than CCI days
  - CCI lasting less than CCI days
  - CCI lasting less than CCI days
- CCI × upper limit of normal (ULN) with concurrent increase in CCI CCI × ULN without evidence of CCI CCI
- Any CCI toxicity, excluding the following:
  - CCI mmol/L) for less than 1 week
  - CCI that is considered clinically insignificant by the Investigator and resolves within CCI hours with appropriate medical management
  - CCI lasting less than CCI hours
  - CCI lasting less than CCI hours
  - CCI lasting less than CCI days
  - CCI , unless CCI is present
  - CCI (first occurrence and in the absence of CCI that does not resolve within CCI with appropriate clinical management)

For subjects in Arm 6, the DLT criteria also includes the following

- CCI or symptomatic with a CCI

For subjects in Arm 7, the DLT criteria also includes the following

- CCI
- CCI
- CCI if accompanied by CCI CCI

- In subjects without CCI metastases, CCI × ULN lasting CCI days
- In subjects with CCI metastases, CCI × ULN lasting CCI days, if the baseline level was CCI × ULN
- In subjects with CCI metastases, CCI × ULN lasting CCI days, if the baseline level was CCI × ULN

Only evaluable subjects will be included in the assessment of the number of DLTs and DLTs will be evaluated for each arm.

A DLT-evaluable subject for safety is defined as a subject who has received the full prescribed dose of durvalumab and who has received:

- CCI of the prescribed number of doses of paclitaxel and of the novel oncology therapy during Cycle 1 (weeks 0 through 3). They must also have completed the first 28-day cycle or have had a DLT during the first 28-day cycle (Arms 2 through 5)
- The prescribed dose of DS-8201a or Dato-DXd therapy, respectively, during Cycle 1 (weeks 0 through 2). They must also have completed the first 21-day cycle or have had a DLT during the first 21-day cycle (Arms 6 and 7)

While rules for adjudicating DLTs are specified above, an AE that is any grade or listed as exempt above may also be defined as a DLT by the Investigator, based on the emerging safety profile of durvalumab and the novel oncology therapies. Likewise, subjects who become non-evaluable for DLT because they discontinued or interrupted treatment due to toxicities other than DLTs may be counted as DLT subjects. Subjects who are not evaluable for toxicity can be replaced in order to have 6 DLT-evaluable subjects to determine the RP2D but they will still be included in the SAF.

3.3.3.2 DLT-equivalent toxicity events (DETs)

DETs are AEs that fulfil the DLT criteria but occur:

- During or beyond cycle 2 in the 6-subject safety run-in group of a treatment arm that has passed the safety run-in
- During any cycle for subjects not treated within the 6-subject safety run-in

DETs will be assessed in subjects who are defined to be DLT-evaluable in Cycle 1.

3.3.4 Treatment exposure

Exposure variables comprise the measure of treatment durations, counts and dose intakes. Further details on the below sections are provided in Appendix 8.2.

3.3.4.1 Duration of treatment exposure

Intended treatment duration (Total treatment duration)

The intended treatment duration (also known as total treatment duration) of a subject to a drug or therapy is calculated using the start and stop dates of the drug/therapy and the intended dosing interval (or intervals if dosing is not regular). For a dosing period for the drug/therapy, the intended treatment duration is calculated as the number of days from date A to date B (i.e. B – A + 1) where

- A is the date of first dose of the study drug/therapy in the dosing period
- B is the earliest of:
    - The date of death
    - The date of DCO, and
    - The date when the last non-zero dose of the study drug/therapy was received (e.g. >0 mg of durvalumab, paclitaxel or the novel oncology therapy (including capivasertib)) plus C, where C is equal to the scheduled number of days between doses minus one. Values for C for the study drugs/therapies in each arm of this study are shown in
    - Table 15. Further details on the values for C can be found in Appendix 8.1

Table 15: Values based on dosing interval (C) used in the calculation of treatment exposure

Drug/Therapy	Arm 1	Arm 2	Arm 4	Arm 5	Arm 6	Arms 7/8
durvalumab[a] (all cohorts)	27	27	27	27	20	20
paclitaxel[b] (all cohorts)	6 or 13	6 or 13	6 or 13	6 or 13	-	-
capivasertib (Cohort dose level: 1, -1; Individual dose level: 1, -2)	-	0 or 3 or 10[c]	-	-	-	-
oleclumab (Cohort dose level: 1, -1; Individual dose level: 1)	-	-	-	13 or 27[d]	-	-
DS-8201a (Cohort dose level 1, -1: Individual dose level: 1, -1, -2)	-	-	-	-	20[e]	-

Dato-DXd (datopotamab deruxtecan)	-	-	-	-	-	20[f]

[a] durvalumab is scheduled to be given once q4w for Arms 1 through 5 and q3w in Arm 6
[b] paclitaxel is scheduled to be given in 4-week cycles: 3 weeks once weekly (D1, D8 and D15) and 1 week off. C=6 if the last dose was the scheduled Day 1 or 8 dose of a cycle, and C=13 if the last dose was the scheduled Day 15. This is the same in all arms
[c] capivasertib is scheduled to be given bid in 4-week cycles: 4 days on (D2, D3, D4 and D5) and 3 days off for 3 weeks, and the final week of the cycle off. C=0 if the last dose was the scheduled Day 2, 3, 4, 9, 10, 11, 16, 17 or 18 of a cycle; C=3 if the last dose was the scheduled Day 5 or 12 of a cycle; and C=10 if the last dose was the scheduled Day 19 of a cycle
[d] oleclumab is scheduled to be given in 4-week cycles: q2w for the first 2 cycles (D1 and D15 of cycle 1 and 2), then q4w starting at cycle 3 (D1). C=13 if the last dose was the scheduled Day 1 or 15 of cycle 1 and 2, and C=27 if the last dose was the scheduled Day 1 of cycle 3 and all future cycles
[e] DS-8201a is scheduled to be given in 3-week cycles
[f] Dato-DXd is scheduled to be given in 3-week cycles

Actual treatment duration

Actual treatment duration (days) will be calculated separately for the study drugs (durvalumab, paclitaxel and the novel oncology therapies) as follows:

Actual treatment duration = intended treatment duration (days) – (total duration of dose delays (days) + total duration of dose interruptions (days)), where intended treatment duration will be calculated as above. Note that for study drugs with intermittent dosing schedules, the planned no-dose periods will be excluded from the interruption duration in this calculation. Note that infusion interruptions (where at least some dose was given, i.e. infusion volume at start of exposure – infusion volume at end of exposure > 0) are not included in this calculation.

Dose reductions for durvalumab are not permitted and the calculation of actual treatment duration makes no adjustment for any dose reductions that may have occurred.

3.3.4.2 Exposure counts

Number of doses received

For durvalumab and the novel oncology therapies, exposure will also be measured by the number of doses received. For paclitaxel, exposure will also be measured by the number of infusions received, number of cycles received and number of subjects receiving planned starting dose.

Cycles of treatment with durvalumab are of 4 weeks duration (Arms 1 through 5) or 3 weeks duration (Arms 6 through 8) with a single dose on day 1 of each cycle.

Cycles of treatment with paclitaxel are of 4 weeks duration: 3 weeks on (administered once weekly on days 1, 8 and 15) and 1 week off.

Cycles of treatment with the novel oncology therapies are as follows: capivasertib 4 weeks duration: 3 weeks on (administered on days 2 through 5) and 1 week off); oleclumab 2 weeks duration for 2 cycles then 4 weeks duration from cycle 3; DS-8201a and Dato-DXd 3 weeks duration with a single dose on day 1 of each cycle, respectively.

Delays, reductions and interruptions

Treatment dose delays, dose interruptions and dose reductions (reductions are N/A for durvalumab) are measured for all study drugs. The number of infusion interruptions is also calculated for infusion-administered drugs. Details of these are provided in Appendix 8.2.

Subjects who permanently discontinue during a dose interruption
If a subject permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded, with dose >0, will be used in the calculation of exposure. The dose interruption will not be included as a dose interruption in the summary tables but will be recorded in the listing for dosing.

3.3.4.3 Dose intake

Dose intensity

Dose intensity will be derived separately for durvalumab, paclitaxel and the novel oncology therapies.

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. As all study drugs may not necessarily discontinue at the same time, RDI will be calculated using the exposure for each drug separately within a treatment arm for each subject. RDI will be defined as follows:

RDI = 100% * d/D, where:

- d is the actual cumulative dose delivered up to the actual last day of dosing for that drug, and

- D is the total dose of that drug that would be delivered, if there were no modifications to dose or schedule except planned reductions. Further details, including the formulae for d and D, are provided in Appendix 8.2.

When deriving actual dose administered for infusion administered medications, the volume before and after infusion will also be considered.

For capivasertib, which is administered orally at a dose of 400mg bid, a dose will constitute a one tablet (200mg), and so a whole day's worth of dosing is considered four doses.

Calculated average dose intake

Calculated average dose intake for infusion administered medications, durvalumab and novel oncology therapies, where:

- Calculated average dose intake per subject = average over all cycles [((sum([infusion volume at start of exposure – infusion volume at end of exposure]/infusion volume at start of exposure))/number of doses subject received)*100]
- If the subject does not receive a dose this will not be included in their average calculated dose intake

3.3.5 Laboratory measurements

Blood and urine samples for the determination of clinical chemistry, hematology, coagulation and urinalysis will be collected as described in Section 8.2.1 of the CSP.

For the derivation of baseline and post-baseline visit values, the rules described in Section 3.6 of this document considering definition of baseline, visit windows and how to handle multiple records will be used.

Change from baseline in hematology and clinical variables will be calculated for each post-dose visit on treatment. CTCAE grades will be defined at each visit according to the CTCAE grade criteria using project ranges, after conversion of lab result to corresponding project-wide preferred units.

Corrected calcium product will be derived using the following formula:

Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – albumin (G/L)] × 0.02)

Absolute lymphocyte count (ALC) can be programmatically derived if not reported using the reported Lymphocytes % and Total white cell count as follows:

ALC = Total white cell count x Lymphocytes %

The denominator used in laboratory summaries will only include evaluable subjects (i.e. those who had sufficient data to have the possibility of an abnormality). For example:

- If a CTCAE criterion involves a change from baseline, evaluable subjects would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline to be evaluable, the subject need only have 1 post-dose value recorded

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or on limits of range), and high (above range).

The maximum or minimum on-treatment (i.e. assessments between date of start dose and 90 days following discontinuation of IP) value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time. Local reference ranges will be used for the primary interpretation of laboratory data at the local laboratory. Project reference ranges will be used for reporting purposes.

3.3.6 Physical examinations

Physical examinations will be performed as described in Section 8.2.2 of the CSP. Abnormalities recorded prior to the first dose of study treatment will be recorded as part of the subject's baseline signs and symptoms. Abnormalities first recorded after first dose of study treatment will be recorded as AEs unless unequivocally related to the disease under study.

3.3.7 Electrocardiograms

Resting 12-lead electrocardiograms (ECGs) will be recorded at screening and as clinically indicated throughout the study as described in Section 8.2.4 of the CSP.

The following ECG variables will be collected: QTcF, ECG mean heart rate, PR duration QRS duration, QT duration, RR duration, and overall ECG evaluation.

The overall evaluation of an ECG will either be "normal" or "abnormal" with abnormalities categorized as either "clinically significant" or "not clinically significant". In case of clinically significant ECG abnormalities, 2 additional ECGs will be obtained over a brief period (e.g. 30 minutes) to confirm the finding.

Where QTcF (Fridericia) is not reported, it will be calculated programmatically using the reported ECG values (RR and QT) as follows (where RR are in seconds):

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Alternatively, RR (or QT) can be programmatically derived if not reported but QTcF and QT (or RR, respectively) is reported. RR can be calculated as follows:

$$\boldsymbol{RR = \left(\frac{QT}{QTcF}\right)^3}$$

3.3.8 Vital signs

The following vital signs will be measured as described in Section 8.2.3 of the CSP: Systolic and diastolic blood pressure (BP), pulse rate, temperature, and respiratory rate. Body weight will also be recorded along with vital signs.

For the derivation of baseline and post-baseline visit values, the definitions and rules described in Section 3.6 for visit windows, and how to handle multiple records will be used.

3.3.9 Eastern Cooperative Oncology Group performance status

Eastern Cooperative Oncology Group (ECOG) performance status (PS) will be assessed as described in Section 8.2.8 of the CSP as the following:

0. Fully active; able to carry out all usual activities without restrictions
1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (e.g. light housework or office work)
2. Ambulatory and capable of self-care, but unable to carry out any 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; unable to carry out any self-care and totally confined to bed or chair
5. Dead

Any significant changes from baseline or screening will be reported as AE.

3.4 Pharmacokinetic variables

Pharmacokinetic concentration data will be collected as described in section 8.5.1 of the CSP.

No formal non-compartmental analysis will be conducted for durvalumab or the novel oncology therapies since the PK sampling scheme is sparse and would not allow for meaningful determination of PK parameters.

3.5 Other variables

3.5.1 Baseline characteristics

Baseline characteristics that will be collected or derived are:

- Demographics: Age (years), sex, race, and ethnicity
- Subject characteristics: Weight, height and body mass index (BMI)

- Disease characteristics at initial diagnosis: Diagnosis date, primary tumor location, histology type, tumor grade, TNM classification, American Joint Committee on Cancer (AJCC) staging, WHO/ECOG performance status

- Extent of disease upon entry to study: Stage (locally advanced, metastatic, both) and site of local/metastatic disease, recent progression date

- Medical history: Name of past and/or concomitant diseases (verbatim and coded using the latest or current version of the MedDRA dictionary), start and stop dates

- Surgical history: Surgical procedure (verbatim and coded using the latest or current version of the MedDRA dictionary) and date of surgery

- Prior radiotherapy: Site/region treated location, treatment setting, site/region laterality, classification of treated site/region, type of radiotherapy, radiotherapy technique

- Prior cancer therapy: Therapy class, treatment setting

- Pregnancy status for applicable subjects only: Test date and result (positive or negative)

3.5.2 Prior and concomitant medications and therapies

All therapies (drug and non-drug), including herbal preparations, whether prescribed or over-the-counter, that are used during the study will be recorded on the eCRF. Details include generic and/or brand names of the medications, World Health Organisation Drug Dictionary (WHO-DD) encoding (using the latest of current WHO-DD version), reason for use, route, dose, dosing frequency, and start and stop times.

Prior medications are defined as those taken prior to study treatment with a stop date prior to the first dose of study treatment.

Concomitant therapies are defined as those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment). Concomitant medications administered as treatment for drug-related AESIs will be recorded until either event resolution, end of study, trial termination, withdrawal of consent, or subject death.

Missing start and stop dates for medications will be handled using the rules described in Section 3.6.3.

3.5.3 Immunogenicity variables

Serum samples for antidrug antibodies ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits shown in

the CSP (Section 8.5.1.2). ADA results from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well.

The percentage of ADA-positive subjects in each of the categories will be calculated, using the number of subjects in the ADA-evaluable set (defined in Section 2.1.4) of the treatment arm as the denominator. A subject is defined as being ADA positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise ADA negative.

- ADA positive at any visit; the percentage of ADA-positive subjects in the ADA-evaluable set is known as ADA prevalence
- The sum of both treatment-induced and treatment-boosted ADA; the percentage of subjects fulfilling this criterion in the ADA analysis set is known as ADA incidence
- ADA positive post-baseline and positive at baseline
- ADA positive post-baseline and not detected at baseline (treatment-induced ADA)
- ADA not detected post-baseline and positive at baseline
- Treatment-boosted ADA, defined as a baseline positive ADA titer that was boosted to a 4-fold or higher level (greater than the analytical variance of the assay) following drug administration
- Persistently positive ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement. or an ADA positive result at the last available assessment. The category includes subjects meeting these criteria who are ADA positive at baseline
- Transiently positive ADA, defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive. The category includes subjects meeting these criteria who are ADA positive at baseline

3.5.4 Biomarker variables

Samples for the determination of biomarkers will be taken from all enrolled subjects according to the schedule described in Section 8.8 of the CSP.

Biomarker status will be assessed for evaluable subjects in each cohort. This includes PD-L1 for all Arms, Phosphoinositide-3-kinase, catalytic, alpha polypeptide (PIK3CA) for Arm 2 (durvalumab + paclitaxel + capivasertib), CD73 for Arm 5 (durvalumab + paclitaxel + oleclumab) and local human epidermal growth factor receptor 2 (HER2) for Arm 6 (durvalumab + DS-8201a).

3.5.5 Echocardiograms/multiple gated acquisition scans

Echocardiograms/multiple gated acquisition (ECHO/MUGA) scans will be performed as described in Section 8.2.5 of the CSP.

Left ventricular ejection fraction (LVEF) will be measured by either ECHO or MUGA scan.

3.5.6 CCI

CCI

3.6 Other information regarding the derivation of primary and secondary variables

3.6.1 Definition of baseline

For efficacy endpoints the last observed measurement prior to randomization is considered the baseline measurement. For time to event endpoints such as PFS and OS and for calculation of the number of days on study, the start date (Day 1) will be the date of the first dose of study treatment, namely the earliest start date of durvalumab, paclitaxel, or novel oncology therapy. See Sections 3.2.2 and 3.2.5 for more detail.

For all other variables, baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP (i.e. the latest result obtained prior to the start of study treatment). For continuous laboratory variables, ejection fraction measurements, ECG and vital signs, if two visits are equally eligible to assess subject status at baseline (e.g. screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average will be used as the baseline value. In the scenario where there are two assessments on the day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarized over time, time on study will be calculated in relation to date of first study treatment.

3.6.2 Time windows for safety data

Time windows will be defined for all presentations of safety data that summarize values by visit according to the following conventions:

- The time windows should be exhaustive so that data recorded at any time point (scheduled or unscheduled) has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit

- The window for visits following baseline will be constructed in such a way that the upper limit of the interval falls half-way between the two visits (the lower limit of the first post baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day. For demonstration purposes, Table 16 shows the visit windows for vital signs up to week 50 for Arm 1. Note that the visit windows for the different treatment arms differ due to frequency of certain assessments e.g. ECG, hematology. Assessments will continue until study end as defined in the CSP.

Table 16: Analysis visits and visit windows

Cycle	Scheduled day	Analysis window (day)
Cycle 1	Day 1	See section 3.6.1 for baseline definition
	Day 15	2 to 22
Cycle 2	Day 29	23 to 43
Cycle 3	Day 57	44 to 71
Cycle 4	Day 85	72 to 99
Cycle 5	Day 113	100 to 127
Cycle 6	Day 141	128 to 155
Cycle 7	Day 169	156 to 183
Cycle 8	Day 197	184 to 211
Cycle 9	Day 225	212 to 239
Cycle 10	Day 253	240 to 267
Cycle 11	Day 281	268 to 295
Cycle 12	Day 309	296 to 323
Cycle 13	Day 337	324 to 351

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval)

- Listings will display all values contributing to a time point for a subject

- For visit-based summaries, if there is more than one value per subject within a time window then the closest value to the scheduled visit date will be summarized. If the values are equidistant from the nominal visit date, then the earlier value will be used. Data listings will highlight the values used in the summary table, wherever feasible. Note: in summaries of extreme values, all post-baseline values collected are used including those collected at unscheduled visits regardless of which value is closest to the scheduled visit date

- For summaries at subject level, all values will be included when deriving a subject level statistic such as a maximum regardless of whether or not they appear in the corresponding visit-based summary

- In general, the formula for calculating the visit window upper bound for $visit_n$ is as follows

    - If $visit_{n+1} + visit_n$ is **EVEN** then the upper bound for $visit_n$ is $(visit_{n+1} + visit_n)/2$

    - If $visit_{n+1} + visit_n$ is **ODD** then the upper bound for $visit_n$ is $floor((visit_{n+1} + visit_n)/2)$

- The end of treatment visit will be slotted to the appropriate on treatment visit according to the windowing schedule

3.6.3 Handling of missing data

Missing data will generally not be imputed.

Safety assessments of the form of "<x" (i.e. below the lower limit of quantification) or ">x" (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but will be displayed at "<x" or ">x" in the listings.

Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug with the exception of causality assessments that are not applicable for the subject, e.g. causal relation to capivasertib for subjects in Arm 1.

For missing start dates for AEs and concomitant medications/procedures, the following will be applied:

- Missing day: Impute the 1st of the month unless month is the same as month of first dose of study drug then impute first dose date

- Missing day and month: Impute 1st January unless year is the same as first dose date then impute first dose date

- Completely missing date: Impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date

When imputing a start date, ensure that the new imputed date is sensible e.g. is prior to the end date of the AE. For missing stop dates of AEs or concomitant medications/procedures, the following will be applied:

- Missing day: Impute the last day of the month unless month is same month as last dose of study drug then impute last dose date

- Missing day and month: Impute 31st December unless year is the same as last dose date then impute last dose date

Subjects with a partial date of birth (i.e. for those countries where year of birth only is given) will have the 1st of the month imputed if the day is missing, and 1st Jan imputed if the day and month is missing.

4 ANALYSIS METHODS

A formal analysis of the final data will be performed after data cut-off (DCO). The DCO for final analysis for subjects on Arms 1, 2, 5, and 6 will be performed when the last subject has had the opportunity to be followed up for approximately 12 months from the date of first dose. The final analysis for subjects on Arm 7 and 8 will be performed when the last subject has had the opportunity to be followed for at least 6 months from the date of first dose. All study endpoints, including OS, will be followed-up until DCO after the last subject is treatment assigned.

4.1 General principles

The general principles that will be followed throughout the study include the following:

- All analysis and reporting will be by treatment arm. If any treatment arm has multiple cohort dose levels, then these will be analyzed separately and a total column will be presented for the treatment arm

- All safety data will be summarized using the SAF. Evaluations of safety and tolerability will include, but may not be limited to, analyses of the safety variables detailed in Section 3.3 using appropriate summary statistics

- Efficacy endpoints (secondary and exploratory) detailed in Section 3.2 will be summarized and analyzed as appropriate using the FAS or response evaluable analysis set (ORR and BoR)

- PK data will be summarized and analyzed using the PK analysis data set

- ADAs will be analyzed using the ADA evaluable subjects of the SAF

- The analyses will be descriptive, and no inferential analysis will be performed based on statistical tests. All evaluations will be exploratory in nature

- Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category

- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm. Overall totals will be calculated for baseline summaries only

- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data

- For categorical data, percentages will be rounded to 1 decimal place

- SAS® version 9.3 or higher will be used for all analyses

- Exact 95% CIs for proportions will be calculated using the Clopper-Pearson method

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

- For point-estimates of survival based on the Kaplan-Meier method, CIs will be calculated using the default method available in the SAS LIFETEST procedure (i.e. using Greenwood's estimate of standard-error and a log-log transformation).

- For treatment arms that do not reach the RP2D, listings may be produced of the data to summarize the top-line demographic, efficacy and safety data

4.2 Study population

4.2.1 Disposition of subjects

The following will be presented by treatment arm:

- Number and percentage of subjects who were screened, who received and did not receive study medication, who discontinued treatment and the reason for discontinuation
- Number and percentage of subjects in each analysis set
- Subject recruitment by country and center

4.2.2 Protocol deviations

Important protocol deviations are defined in Section 2.2 and will be listed by treatment arm and summarized separately by treatment arm for all subjects assigned to treatment.

The number and percentage of subjects with any IPD will be summarized for each IPD category. Subjects with more than one deviation in the same IPD category will be counted once for that IPD category. Any subjects who have deviations in more than one IPD category will be counted once in the overall summary.

4.2.3 Demographic and other baseline characteristics

Demographic and other baseline characteristics (see Section 3.5.1) will be listed for all subjects enrolled and summarized for the FAS using the rules for summarizing continuous and categorical variables described in Section 4.1.

In addition to being summarized as continuous variables, age and weight will be summarized as the following categorical variable: age group (<65, ≥65 – <75, ≥75 years), weight group (<70, ≥70 – ≤90, >90 kg) and BMI group (Underweight [<18.5], Normal [18.5 - <25.0], Overweight [25.0 - <30.0] and Obese [>=30.0].

BMI (kg/m^2) = $Weight/Height^2$

Medical history and surgical history are coded using MedDRA (latest or current version) and will be summarized by System Organ Class (SOC) and Preferred Term (PT).

4.2.4 Prior and concomitant medications and procedures

Prior and concomitant medications and procedures will be listed for all subjects in the FAS.

Medications received prior to, concomitantly, or post-treatment will be coded using the WHO-DD (current or latest version) Anatomical Therapeutic Chemical (ATC) classification codes.

Concomitant medications will be summarized for the FAS by ATC classification codes. Subjects with the same concomitant medication/procedure multiple times will be counted once per medication/procedure. A medication/procedure that can be classified into more than one chemical and/or therapeutic subgroup will be presented in each subgroup.

4.2.5 Study drug administration

Individual subject data for study drug administration will be listed for all subjects receiving study drug.

4.3 Analysis of efficacy

The efficacy analyses described in this section are secondary/exploratory and will be performed for subjects in the FAS (DoR, PFS, change in tumor size, OS) or response evaluable analysis set (ORR and BoR) by treatment arm.

All individual efficacy response data will be listed.

For all efficacy analyses associated with RECIST 1.1 assessments (ORR, PFS, DoR, percentage change in tumor size), subjects continuing in the study (on/off treatment) will be censored at the point scans are no longer collected.

4.3.1 Objective response rate

The ORR will be estimated and presented with the corresponding exact 95% Clopper-Pearson CIs. Owing to the CCI design and the possibility of early termination, the ORR is biased if the trial continues to the second stage (Porcher and Desseaux, 2012). Thus, for treatment arm 6 (durvalumab + DS-8201a) and any others arms which continue to Part 2, exact 95% mid-p CIs will be reported instead of Clopper-Pearson CIs.

The response evaluable analysis set will be used for the analysis of ORR using a denominator as specified in section 3.2.1. The number (%) of subjects with a single visit response (i.e. an unconfirmed response) will also be presented for Part 1, and as a sensitivity analysis of the for the final analysis of ORR. For each treatment arm, BoR will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

4.3.2 Progression free survival

The number (%) of subjects in the FAS who were on treatment or who had discontinued treatment will be provided separately for those subjects who had and had not experienced disease progression.

Kaplan-Meier plots and descriptive statistics will be provided separately for PFS by treatment arm for the FAS. Summary statistics will include: lower and upper quartile and median PFS for all study arms.

For Part 2, PFS at 6 months will also be summarized (using the Kaplan-Meier plot) and presented by treatment arm.

4.3.3 Duration of response

Descriptive data will be provided for the DoR for responding subjects in the FAS (Section 3.2.1), including Kaplan-Meier curves (without any formal comparison or p-value attached). Summary statistics will include: lower and upper quartile and median DoR. A swimmer plot will be produced for each treatment arm to graphically display the duration of response.

4.3.4 Overall survival

The following number (%) of subjects in the FAS will be presented by treatment arm: those who have died, those still in survival follow-up, those lost to follow-up, those who withdrew consent, and those with censored OS (i.e. those whose survival status was not defined at DCO).

Kaplan-Meier plots and descriptive statistics will be presented for OS by treatment arm for the FAS. Summary statistics will include the lower and upper quartile and median OS.

4.3.5 Percentage change in tumor size

Descriptive statistics will be provided for the absolute value, change from baseline and percentage change from baseline in tumor size for subjects in the FAS. Waterfall plots and spider plots will be provided for each treatment arm. All scheduled and unscheduled RECIST 1.1 assessments will be included in the waterfall plots and spider plots. The visits included in the summary of descriptive statistics will be based on the following windowing rule.

Apply a window around the week X visit: Whenever tumor size data for the week X visit (Note: or visit at which progression was documented if before week X) is available then this should be used in the analysis. A windowing rule will be applied and will follow the protocol allowed visit window; therefore, any RECIST scan performed within +/- 1 week of the protocol scheduled visit will be used for that visit. For example, if X=8, a scan occurring anytime from week 7 to 9 (inclusive) would be used as the week 8 visit. If after data entry query it arises that two assessments have taken place in the same window, then the assessment that occurred closest to the scheduled day (i.e. exactly 8 weeks post-treatment assignment) will be included in this summary. If two visits are equidistant from the scheduled day, the earliest of the two visits will be included in this summary.

4.3.6 Duration of follow-up

Descriptive statistics and categories will be used to summarize the duration of follow-up for subjects in the FAS.

4.4 Analysis of safety

Safety data will be assessed in terms of AEs, physical examination, clinical chemistry, hematology, coagulation, urinalysis, vital signs and ECGs.

AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by subject. The number of subjects experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced.

Other safety data will be assessed in terms of clinical chemistry, hematology, coagulation and vital signs and summarized using appropriate summary statistics. Exposure to durvalumab + paclitaxel combination therapy, durvalumab + paclitaxel + novel oncology therapy combinations, durvalumab + DS-8201a, and durvalumab + Dato-DXd will be summarized. Time on study, time on the combination therapy, and (for applicable treatments) dose delays, dose reductions, dose interruptions and infusion interruptions will also be summarized.

4.4.1 Adverse events

All AEs, both in terms of MedDRA preferred term and CTCAE grade, will be listed and summarized descriptively by count (n) and percentage (%). The MedDRA dictionary (latest or current version) will be used for coding.

TEAEs observed up until 90 days following discontinuation of study treatment (including treatment through progression) or until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first) will be used for reporting in all AE summary tables.

Pre-treatment AEs and AEs that occur after a subject has received further therapy for cancer (following discontinuation of IP but within 90 days) will be included in the AE listings. A separate listing for AEs for arms that do not pass the safety run-in may also be produced.

All reported AEs will be listed along with the date of onset (including study day), date of resolution (if AE is resolved), investigator's assessment of CTCAE grade and relationship to study drug. Multiple events per subject will be counted once.

Summary information (the number and percent of subjects by treatment arm) by SOC and PT will be tabulated for:

- All AEs
- All AEs possibly related to study medication (as determined by the reporting investigator). These will also be broken down by causal IP agent

- AEs with CTCAE grade 3 or 4
- AEs with CTCAE grade 3 or 4, possibly related to study medication (as determined by the reporting investigator). These will also be broken down by causal IP agent
- Most common AEs (frequency of >5%) with CTCAE grade 3 or 4
- AEs with outcome of death
- AEs with outcome of death possibly related to study medication (as determined by the reporting investigator). These will also be broken down by causal IP agent
- All SAEs
- All SAEs possibly related to study medication (as determined by the reporting investigator). These will also be broken down by causal IP agent
- AEs leading to discontinuation of study medication
- AEs leading to discontinuation of study medication, possibly related to study medication (as determined by the reporting investigator). These will also be broken down by causal IP agent
- AEs leading to dose interruption of study medication
- AEs leading to dose interruption of study medication, possibly related to study medication (as determined by the reporting investigator). These will also be broken down by causal IP agent
- AEs leading to hospitalization

For the truncated AE tables of most common AEs, all events that occur in at least 5% of subjects overall will be summarized by preferred term, by decreasing frequency. This cut-off may be modified after review of the data. When applying a cut-off (e.g. 5%), the raw percentage should be compared to the cut-off, no rounding should be applied first (i.e. an AE with frequency 4.9% will not appear if the cut-off is 5%).

Adverse events of special interest and adverse events of possible interest

Preferred terms used to identify AESIs and AEPIs (as defined in Section 3.3.2) will be listed before DBL and documented in the Trial Master File. Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI grouping per IP. Groupings will be based on preferred terms

provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided per IP.

The number (%) of subjects who have at least one AESI/AEPI (by grouped term and preferred term) will be presented by treatment group.

An overall AESI/AEPI summary will be presented, including number and percentage of subjects in each of these categories.

The number (%) of subjects who have at least one AESI will be presented by treatment group.

The number and percentage of subjects by treatment arm will also be tabulated for infusion reaction AEs, DLTs and DETs.

Infection AEs

The infection AE tables are not planned to be generated for this study. However, if considered necessary at the time of final analysis, infection AEs will be summarized as follows: Infection AEs will be summarized by pooled terms and PTs in two ways: (1) using MedDRA HLGT/HLT pooled terms (2) Custom pooled terms (pneumonia, sepsis and urinary tract infections). The following summaries will be reported for both HLGT/HLT pooled terms and custom pooled terms and PTs:

- Infection AEs (including event rate)
- Infection AEs by maximum reported CTCAE grade
- Serious Infection AEs
- Infection AEs presented by outcome
- Infection AEs of maximum CTCAE grade 3 or 4
- Infection AEs with outcome of death
- Infection AEs leading to discontinuation of any study treatment
- Infection AEs leading to dose delay/interruption of any study treatment

An overall infection AE summary will be presented, including the number and percentage of subjects in each of these categories, and additionally causally related infection AEs, causally related serious infection AEs, causally related infection AEs of maximum CTCAE grade 3 or 4, causally related infection AEs with outcome of death, causally related infection AEs leading to discontinuation of any study treatment.

4.4.2 Summary of long-term tolerability

To assess long-term tolerability, if there are sufficient subjects with events to warrant it, prevalence plots, life plots and cumulative incidence plots may be presented for each of the AESI grouped terms and any other events considered important after review of the safety data, provided there are ≥10 events, that is 10 events per each treatment arm.

A prevalence plot provides information on the extent to which the events may be an ongoing burden to subjects. The prevalence at time t after the first dose of study treatment is calculated as the number of subjects experiencing the event divided by the number of subjects receiving study treatment or in the safety follow-up at time t; generally, t is categorized by each day after dosing. The prevalence over time may be plotted and presented. Multiple occurrences of the same event are considered for each subject, but a subject is only counted in the numerator whilst they are experiencing one of the occurrences of the event. These plots may only be produced for AESIs that have ≥10 events, that is 10 events per each treatment arm.

A life table can be used to describe the time to onset (date of onset – start date of treatment + 1) of the event and specifically when subjects are most at risk of first experiencing the event. The hazard, or in other words the probability of having an AE in a specified time-period (e.g. 0 – 1 months, 1 – 3 months, 3 – 6 months, etc.) given that the subject reaches that time-period without having an event is plotted for each time-period. These plots may only be produced for AESIs that have ≥10 events, that is 10 events per each treatment arm.

A cumulative incidence plot is a plot of the raw cumulative incidence and cumulative incidence function over time, these may be presented on separate plots. The raw cumulative incidence is the actual probability that a subject will have experienced their first occurrence of the event by a given time-point. These plots may only be produced for AESIs that have ≥10 events, that is 10 events per each treatment arm.

4.4.3 Exposure

Exposure will be listed and summarized for the SAF. The following summaries will be produced:

- Intended treatment duration (Total exposure) separately for durvalumab, the novel oncology therapies, and paclitaxel
- Actual exposure of durvalumab, paclitaxel and the novel oncology therapies
- Actual exposure plot over time showing a line for each treatment arm
- Summary statistics (mean, standard deviation, median, quartiles, minimum and maximum) of RDI of durvalumab, paclitaxel and novel oncology therapies

- Summary of dose delays, dose interruptions and infusion interruptions, and reasons for dose delays, dose interruptions and infusion interruptions of durvalumab

- Summary of infusion interruptions, dose interruptions, reductions and delays, and reasons for infusion interruptions, dose interruptions, reductions and delays of novel oncology therapies and paclitaxel. Infusion interruption summary is applicable to infusion-administered novel oncology therapies only

- Number of chemotherapy cycles received

- Number of doses of durvalumab and novel oncology therapies received

- Calculated average dose intake for infusion administered medications, durvalumab, paclitaxel and novel oncology therapies

- Swimmer plot for each treatment arm, displaying dosing over time for each IP per subject

4.4.4 Laboratory assessments

Laboratory data obtained until the 90 days after the last dose of study treatment or until the initiation of the first subsequent anti-cancer therapy following discontinuation of study treatment (whichever occurs first) will be used for reporting. This will more accurately depict laboratory toxicities attributable to study treatment only as a number of toxicities up to 90 days following discontinuation of study treatment are likely to be attributable to subsequent anti-cancer therapy.

Absolute values and change from baseline for all continuous hematology, coagulation, clinical chemistry and urinalysis laboratory parameters will be summarized by treatment arm and visit.

Scatter plots (shift plots) of baseline to maximum/minimum value (as appropriate) on treatment may be produced for certain parameters if warranted after data review.

Box-plots of absolute values by week, and box-plots of change from baseline by week, may be presented for certain parameters if warranted after data review.

Shift tables for laboratory values by worst common toxicity criteria (CTCAE) grade will be produced. The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- Hematology: Hemoglobin, Total white cell count, Lymphocytes (absolute count), Neutrophils (absolute count), Platelets

- Clinical chemistry: ALT, AST, Alkaline Phosphatase (ALP), Total bilirubin, Albumin, Magnesium (hypo- and hyper-), Sodium (hypo- and hyper-), Potassium (hypo- and hyper-), Corrected calcium (hypo- and hyper-), Glucose (hypo- and hyper-), Gamma-glutamyl transferase/gamma-glutamyl transpeptidase (GGT), Amylase, Lipase, Creatinine, Creatinine Phosphokinase, Serum Phosphorus

- Coagulation : Activated partial thromboplastin time (aPTT), International normalized ratio (INR), Prothrombin time (PT)

For the parameters with no CTCAE grading that are listed in the CSP, shift tables from baseline to worst value on treatment will be provided. Additional summaries will include a shift table for categorical urinalysis parameters (Bilirubin, Blood, Glucose, Ketones, Protein) comparing baseline value to maximum on treatment value.

The denominator used in laboratory summaries of CTCAE grades will only include evaluable subjects. If a CTCAE criterion involves a change from baseline, evaluable subjects are those who have both a pre-dose and at least 1 post-dose value recorded. If a CTCAE criterion does not consider changes from baseline, evaluable subjects are those who have at least 1 post-dose value recorded.

Hy's law
The following summaries will include the number (%) of subjects who have:

- Elevated ALT, AST, and Total bilirubin during the study.
  - ALT ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.
  - AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, and >20x ULN during the study.
  - Total bilirubin ≥2x – ≤3x, >3x – ≤5x, >5x ULN during the study.
  - ALT or AST ≥3x – ≤5x, >5x – ≤8x, >8x – ≤10x, >10x – ≤20x, >20x ULN during the study.
  - Potential Hy’s Law: ALT or AST ≥3x ULN and total bilirubin ≥2x ULN during the study, irrespective of serum ALP. The onset date of ALT or AST elevation should be prior to or on the date of total bilirubin elevation.

Narratives will be provided in the CSR for subjects who have ALT ≥ 3x ULN plus total bilirubin ≥ 2x ULN or AST ≥ 3x ULN plus total bilirubin ≥ 2x ULN at any visit.

Liver biochemistry test results over time for subjects with elevated ALT (i.e. ≥ 3x ULN) or AST (i.e. ≥ 3x ULN), and elevated total bilirubin (i.e. ≥ 2x ULN) (at any time during treatment i.e. between the start of treatment and up to and including 90 days following the date of last dose) will be plotted. Individual subject data where ALT or AST plus total bilirubin are elevated at any time during treatment will be listed also.

Plots of maximum post-baseline ALT and AST vs. maximum post-baseline total bilirubin, expressed as multiples of ULN, will also be produced with reference lines at 3×ULN for ALT and AST, and 2×ULN for Total bilirubin. In each plot, total bilirubin will be in the vertical axis.

Abnormal Thyroid function
Elevated TSH will be summarized per treatment arm in terms of number (%) of subjects with elevated TSH (higher than the upper normal range), low TSH (lower than lower normal range), elevated TSH post-dose and within normal range at baseline, low TSH post-dose and within normal range at baseline. Shift tables showing baseline to maximum and baseline to minimum will be produced.

4.4.5 Electrocardiograms

Summaries of ECG data will include all data obtained up until 30 days after the last dose of study treatment. Absolute values and change from baseline for ECG heart rate, PR duration, QRS duration, QT duration and RR duration will be summarized by treatment arm.

The number and percentage of subjects with normal and abnormal (not clinically significant and clinically significant) ECG results will be presented as a shift table from baseline to worst evaluation during the study by treatment arm.

A summary of QTcF intervals at any observation on treatment in each of the treatment arms will be presented.

Where ECGs are recorded in triplicate at a visit, an average of each measurement will be taken in order to obtain a single value to be used in the analysis/summaries. Where an average cannot be taken for the categorical variable of overall evaluation, the worst evaluation will be reported for a visit.

4.4.6 Echocardiograms/multiple gated acquisition scans

Summaries of LVEF data will include all data obtained up until 30 days after the last dose of study treatment.

Absolute values and change from baseline for LVEF over time will be summarized by treatment arm.

A listing of key information for LVEF events will be also be produced.

4.4.7 Vital signs

Summaries of vital signs data will include all data obtained up until 30 days after the last dose of treatment.

Absolute values and change from baseline for diastolic and systolic BP, pulse, respiratory rate, and temperature will be summarized by treatment arm.

4.4.8 Eastern Cooperative Oncology Group performance status

Summaries of ECOG data will include all data obtained up until 30 days after the last dose of treatment. Absolute values and change from baseline for ECOG PS will be summarized by treatment arm using a shift plot.

4.4.9 COVID-19

Depending on the extent of any impact, summaries of data relating to subjects diagnosed with COVID-19, and impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study treatment, and other protocol deviations) may be generated, including:

- Disposition (discontinued study treatment due to COVID-19 and withdrew study due to COVID-19)
- Deviations (overall deviations plus if due to COVID-19 and not due to COVID-19)
- Summary of COVID-19 disruptions (visit impact, drug impacted)
- Listing for subjects affected by the COVID-19 pandemic
- Listing for subjects with reported issues in the Clinical Trial Management System due to the COVID-19 pandemic

4.4.10 Ophthalmologic assessments

Ophthalmologic assessments including but not limited to visual acuity testing, slit lamp examination, intraocular pressure measurement, fundoscopy, and fluorescein staining will be performed for Arms 6, 7 and 8. Ophthalmologic assessments will be performed at the visits indicated in CSP schedule of assessments. The ophthalmologic assessment form will be used to assist the licensed eye care provider to assess any ocular surface events. In assessing for corneal toxicity, in addition to CTCAE grading, the following corneal toxicity severity grading scale will be utilized:

- Normal: Clear cornea, no epithelial defects
- Grade 1: Nonconfluent superficial keratitis
- Grade 2: Confluent superficial keratitis, a cornea defect, or 3-line or more loss in best corrected distance visual acuity
- Grade 3: Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse

- Grade 4: Corneal perforation

The number and percentage of subjects with normal and abnormal (not clinically significant and clinically significant) slit lamp and fundoscopy results will be presented as a shift table from baseline to worst evaluation during the study by treatment arm.

4.5 Pharmacokinetic data

PK concentration data for durvalumab and novel oncology therapies will be listed by subject and dosing day/time and will be tabulated using summary statistics for all subjects in the PK analysis set.

If the data are considered suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modeling approach.

A population PK model may be developed using a non-linear mixed-effects modeling approach. The impact of physiologically-relevant subject characteristics (covariates) and disease on PK may be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints may be evaluated. The results of such an analysis will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

4.6 Immunogenicity analysis

ADAs will be analyzed in the ADA-evaluable subjects of the SAF.

A summary of the number and percentage of subjects who develop anti-durvalumab antibodies and anti-novel oncology therapy (as applicable) antibodies in different treatment arms will be presented. Median and range for maximum titer for each treatment arm will be provided.

The immunogenicity titer will be listed for samples confirmed positive for the presence of anti-durvalumab antibodies and anti-novel oncology therapy (as applicable) antibodies. For the novel oncology therapies, ADAs will be evaluated only for the subset that are biologics (i.e. oleclumab and DS-8201a).

ADA data of the form of “<x” or “>x” will be imputed as “x” in the calculation of summary statistics but will be displayed at “<x” or “>x” in the listings.

4.7 Exploratory analysis

Some treatment arms may be open or closed in selected countries during the trial for operational reasons. If this occurs, data may be reviewed by country to evaluate any potential impact on the results.

4.7.1 Biomarker analysis

The relationship of PD-L1 expression to clinical outcomes (including but not restricted to) of PFS, ORR, and OS will be explored.

Candidate biomarker expression data may be compared between pre-treatment and on-treatment samples to assess biological responses to immunotherapy.

Other summaries and analyses for exploratory biomarkers may be documented in a separate analysis plan and will be reported in a separate report outside the CSR.

5 INTERIM ANALYSES

No formal interim analysis is planned.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Correction provided in the SAP with regards to Section 9.4 of the protocol which stated: "Baseline will be the last assessment of the variable under consideration prior to the intake of first dose of IP, and the same holds for all efficacy variables". SAP updated to clarify baseline definitions in line with the TA SAP for open label studies.

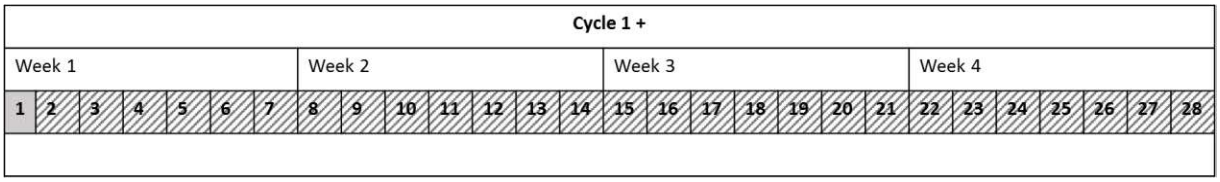
7 REFERENCES

Porcher and Desseaux 2012,
BMC Medical Research Methodology 2012, 12:117

8 APPENDIX

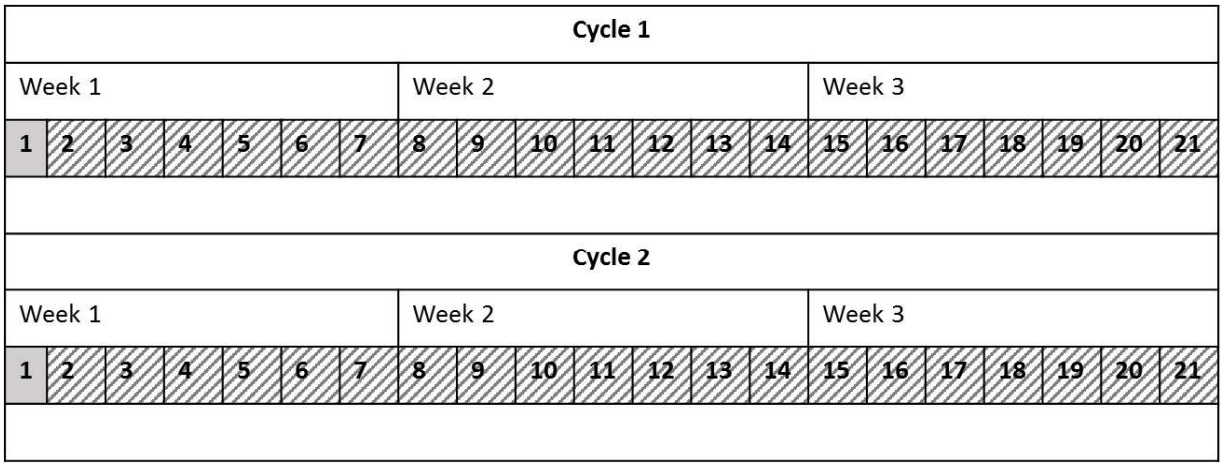
8.1 Deriving the values of the dosing interval (C) used in the calculation of treatment exposure

Durvalumab (Arms 1 through 5)



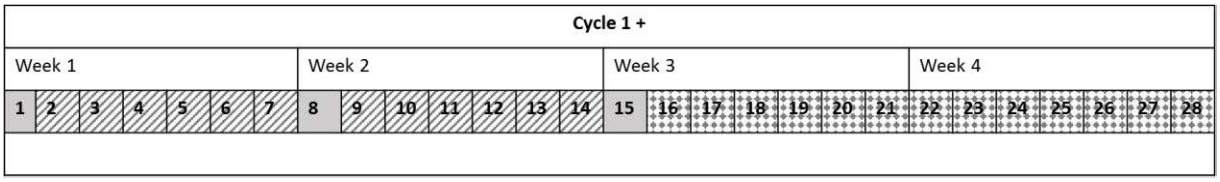
- Scheduled to be given once q4w **(SOLID GREY)**
- C=27 as there are 27 days between each treatment **(DIAGONAL STRIPES)**

Durvalumab (Arms 6 through 8)



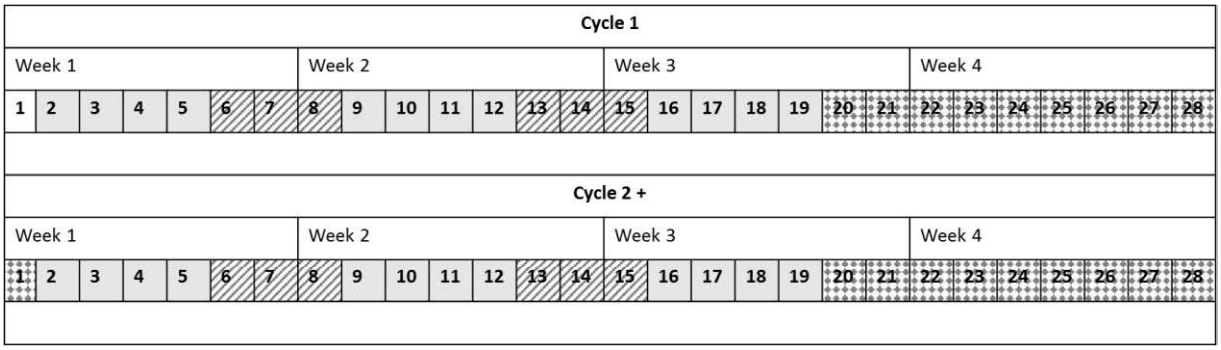
- Scheduled to be given once q3w **(SOLID GREY)**
- C=20 as there are 20 days between each treatment **(DIAGONAL STRIPES)**

Paclitaxel (Arms 1 through 5)



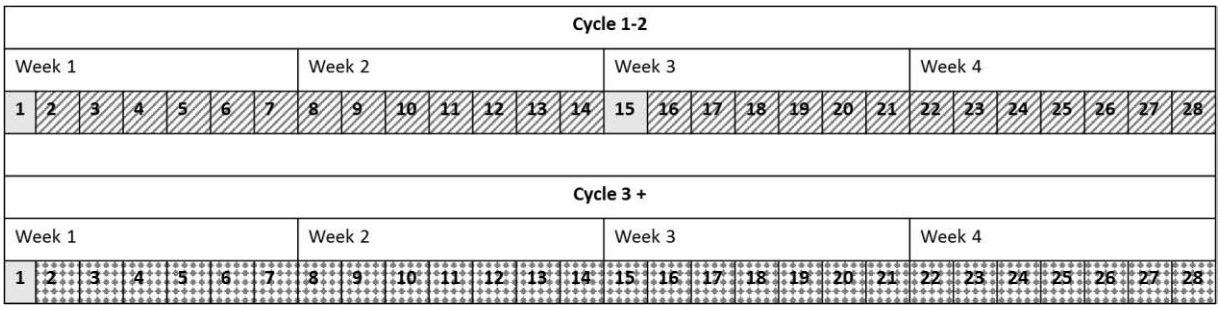
- Scheduled to be given in 4-week cycles: 3 weeks once weekly (D1, D8, D15) and 1 week off **(SOLID GREY)**
- C=6 if the last dose was the scheduled Day 1 or Day 8 dose of a cycle **(DIAGONAL STRIPES)**
- C=13 if the last dose was the scheduled Day 15. This is the same in all arms **(DIAMOND GRID)**

Capivasertib (Arm 2)



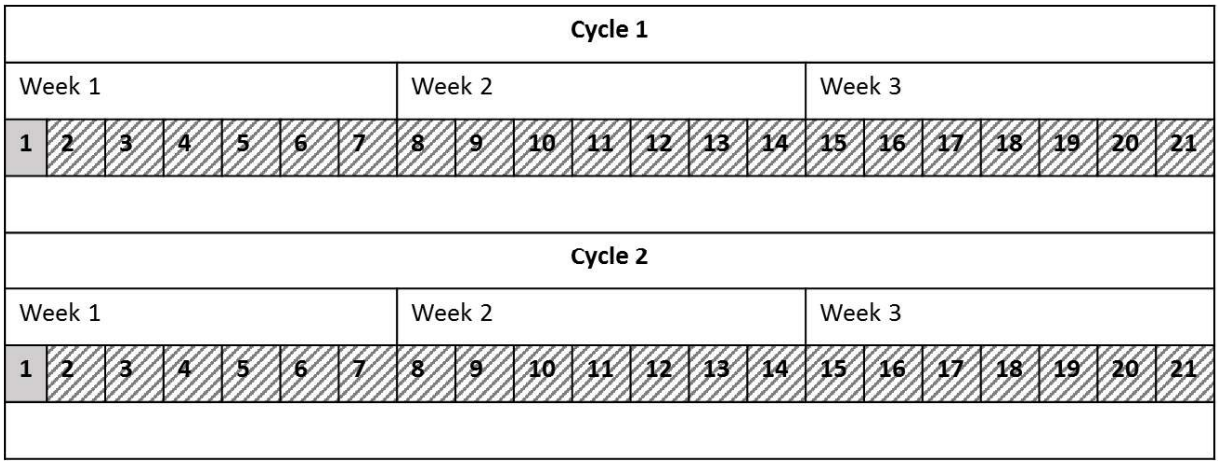
- Scheduled to be given in 4-week cycles: 4 days on (D2, D3, D4 and D5) and 3 days off for three weeks, and the final week of the cycle off **(SOLID GREY)**
- C=0 if the last dose was the scheduled Day 2, 3, 4, 9, 10, 11, 16, 17 or 18 of a cycle
- C=3 if the last dose was the scheduled Day 5 or 12 of a cycle **(DIAGONAL STRIPES)**
- C=10 if the last dose was the scheduled Day 19 of a cycle **(DIAMOND GRID)**

Oleclumab (Arm 5)



- Scheduled to be given in 4-week cycles: q2w for the first 2 cycles (D1 and D15 of cycle 1 and 2), then q4w starting at cycle 3 (D1) **(SOLID GREY)**
- C=13 if the last dose was the scheduled Day 1 or 15 of cycle 1 and 2 **(DIAGONAL STRIPES)**
- C=27 if the last dose was the scheduled Day 1 of cycle 3 and all future cycles **(DIAMOND GRID)**

DS-8201a (Arm 6)



- Scheduled to be given once q3w **(SOLID GREY)**
- C=20 as there are 20 days between each treatment **(DIAGONAL STRIPES)**

Dato-DXd (Arms 7 and 8)

Cycle 1																			
Week 1							Week 2							Week 3					
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Cycle 2																			
Week 1							Week 2							Week 3					
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21

- Scheduled to be given once q3w **(SOLID GREY)**
- C=20 as there are 20 days between each treatment **(DIAGONAL STRIPES)**

8.2 Exposure definitions and calculations

8.2.1 Actual dose intake - definitions

8.2.2 Actual dose intake – infusion-administered drugs

For infusion-administered drugs the study drug dose is typically measured in mg, but the infusion volume before and after is measured in ml. Dose intake calculations are measured in mg using the following formula:

Actual dose intake [mg] = Intended dose [mg]*(1- volume after infusion [ml] / volume before infusion [ml])

Example:
Durva intended dose= 1500mg.
Volume before infusion= 125ml.
Volume after infusion= 25ml.
Actual dose intake= 1500mg*(1-(25ml/125ml)) = 1200mg.

8.2.3 Actual dose intake – orally-administered drugs

For orally-administered drugs (tablets), units other than mg are not used and so the formula becomes:

Actual dose intake [mg] = Exact dose received [mg]

Example:
Capivasertib scheduled 400mg bid (4x200mg tablets (two tablets, 12 hours apart)) on D2, D3, D4, D5, D9, D10, D11, D12, D16, D17, D18, D19 of a cycle.

If subject misses all D9, D10 and D11 tablets and one tablet on D12, then
Actual dose intake for this cycle= 400mg + 400mg + 400mg + 400mg + 0 + 0 + 0 + 200mg + 400mg + 400mg + 400mg + 400mg = 3400mg.

8.3 Exposure counts – definitions

8.3.1 Number of subjects receiving planned starting dose (paclitaxel only)

A subject is considered to have received their planned starting dose of Paclitaxel if the infusion volume before administration is non-zero and the infusion volume after administration = 0.

8.3.2 Dose delay

Total duration of dose delays of paclitaxel is not calculated.

8.3.2.1 Infusion administered study treatment

A treatment cycle is started when >0 dose of durvalumab is administered. As such, a dose delay for durvalumab occurs when the start of a cycle is started at a later date than planned. If durvalumab is delayed, leading to other drugs that were scheduled to be administered on the same day being administered at a later date (but still the same day that durvalumab is eventually administered), then in this instance only durvalumab is classed as being delayed. This is because the other drugs would have been administered on the correct day relative to durvalumab.

A dose delay for all other infusion-administered drugs occurs when the first administration of that drug (>0 dose) in a cycle is administered at a later date relative to the durvalumab dose. Note that if the drug is completely skipped then this is not classed as a delay (it is classed as a dose interruption).

- Total duration of dose delays of durvalumab for Arms 1 through 5 (days) = Sum of all dose delays (days), where a dose delay (days) = max(0,Date of the dose – Date of previous dose – 28 days)

If there are no delays, the duration sums to 0, as infusions are performed on Day 1 of every cycle (28 days)

- Total duration of dose delays of durvalumab for Arms 6 through 8 (days) = Sum of all dose delays (days), where a dose delay (days) = max(0, Date of the dose – Date of previous dose – 21 days)

If there are no delays, the duration sums to 0, as infusions are performed on Day 1 of every cycle (21 days)

Example: C1D1 durvalumab administration = 01-Mar-19, C2D1 durvalumab administration= 10-Apr-19, C3D1= 08-May-19.
Total duration of dose delays of durvalumab = (10-Apr-19 – 01-Mar-19 – 28) + (08-May-19 – 10-Apr-19 – 28)= (40 – 28) + (28 – 28) = 12 days.

- Total duration of dose delays of oleclumab and DS-8201a (days) = Sum of (Date of the dose – Date of durvalumab administration for that cycle)

If there are no delays, the duration sums to 0, as the first infusion of these drugs in a cycle is scheduled on Day 1.

Example: Number of durvalumab delays = 1.
Total duration of dose delays of durvalumab = (10-Apr-19 – 01-Mar-19 – 28) + (08-May-19 – 10-Apr-19 – 28)= (40 – 28) + (28 – 28) = 12 days.

Number of oleclumab delays = 2.
Total duration of dose delays of oleclumab = (03-Mar-19 – 01-Mar-19) + 0 + (09-May-19 – 08-May-19) = 2 + 0 + 1 = 3 days.

Cycle	Day	Drug	Planned date	Actual date
1	1	Durvalumab	01-Mar-19	01-Mar-19
		Oleclumab	01-Mar-19	03-Mar-19
2	1	Durvalumab	29-Mar-19	10-Apr-19
		Oleclumab	10-Apr-19	10-Apr-19
3	1	Durvalumab	08-May-19	08-May-19
		Oleclumab	08-May-19	09-May-19

8.3.2.2 Orally administered study treatment

If capivasertib tablets have not been taken within the +/- 2hour window on a dosing day, the tablets should be skipped, and the next tablets should be taken in adherence to the planned dosing schedule. As such, if capivasertib tablets are not taken on Day 2 and the first dose of capivasertib in that cycle is taken on Day 3, this would be classed as skipping a whole day's dose on Day 2, rather than a delay to capivasertib starting for that cycle. Therefore, delays to capivasertib are not possible.

8.3.2.3 Infusion interruption (infusion-administered drugs only)

An infusion interruption occurs when an interruption occurs during the infusion. The total dose received is >0. The drug can be restarted after the interruption and so it is possible for an infusion interruption to occur and the whole dose to still be administered. If the same infusion was interrupted multiple times, then this would just be captured as one infusion interruption.

The duration of infusion interruptions is not calculated.

8.3.3 Dose interruption

8.3.3.1 Infusion administered study treatment

For infusion-administered drugs, a dose interruption is a temporary interruption during a cycle. That is, during the cycle a dose is completely skipped or is taken at a later date than scheduled. Note that this is only applicable to drugs with multiple doses in a cycle (if the first dose is later than planned it would be a delay).

Total duration of dose interruption of durvalumab is always equal to zero as durvalumab is administered only on Day 1 of each cycle and so dose interruptions are not possible.

For study drugs with intermittent dosing schedules, the planned no-dose periods will be excluded from the duration of dose interruption calculation.

For oleclumab and DS-8201a:

- If a dose during a cycle is administered at a later date than scheduled, the duration of the dose interruption (days) = Date dose was actually received – Date dose was planned to be taken

- If a dose is completely skipped, and it is not the last planned dose of that cycle, then the duration of the dose interruption (days) = Date next dose is received - Date of last dose – (C+1)

- Values of C are provided in Section 8.1

- If a dose is completely skipped, and it is the last planned dose of that cycle, then the duration of the dose interruption (days) = Date of cycle start date + 28 - Date last dose was planned

Example: Number of oleclumab interruptions = 2.
Total duration of dose interruptions for oleclumab = (18-Mar-19 – 15-Mar-19) + (10-Apr-19 + 28 – 24-Apr-19) = 3 + 14 = 17 days.

Cycle	Day	Drug	Planned date	Actual date
1	1	Durvalumab	01-Mar-19	01-Mar-19
		Oleclumab	01-Mar-19	03-Mar-19
	15	Oleclumab	15-Mar-19	18-Mar-19
2	1	Durvalumab	29-Mar-19	10-Apr-19
		Oleclumab	10-Apr-19	10-Apr-19
	15	Oleclumab	24-Apr-19	Skipped
3	1	Durvalumab	08-May-19	08-May-19
		Oleclumab	08-May-19	09-May-19

8.3.3.2 Orally administered study treatment

For capivasertib, a dose is considered as one tablet. On a planned dose day, two tablets are taken twice a day (i.e. a total of four tablets per day). A dose interruption occurs when the total daily dose on a planned dose day= 0, i.e. a subject misses four tablets in one day. If a subject misses one, two or three of the four tablets on a planned dose day, this will not be classed as an interruption. However, it will be accounted for in the dose intake calculations. Capivasertib tablets should not be taken on a planned non-dose day and so a dose interruption for this drug is only recorded if a whole day's dose is completely skipped.

For capivasertib:

- If a whole day of dosing (four tablets) is completely skipped and it is not the last >0 dosing day in the cycle, then the duration of the dose interruption (days) = Date next day of >0 dosing is received - Date the last >0 dosing was received – (C+1)

- Values of C are provided in Section 8.1

- If a whole day of dosing (four tablets) is completely skipped and no more >0 dosing days occur in the cycle, then the duration of the dose interruption (days) = Date of cycle start date + 29 - Date the last >0 dosing was received – 3 – 7

- 10 days is deducted at the end of the above calculation because capivasertib has a planned no-dose period from Day 20 of a cycle to Day 2 of the following cycle

Example: Number of capivasertib interruptions = 2.
Total duration of dose interruptions for capivasertib = 0 + (04-Mar-19 – 02-Mar-19 – (0+1)) + 0 + 0 + (01-Mar-19 + 29 – 05-Mar-19 – 3 – 7) + 0 = 0 + 1 + 14 = 15 days.

Cycle	Day	Drug	Planned date	Actual date
1	1	Durvalumab	01-Mar-19	01-Mar-19
	2	Capivasertib	02-Mar-19	02-Mar-19
	3	Capivasertib	03-Mar-19	Skipped

	4	Capivasertib	04-Mar-19	04-Mar-19, only one tablet taken
	<< all doses received as planned on D5, 9, 10, 11, 12, 16, 17 >>			
	18	Capivasertib	05-Mar-19	05-Mar-19
	19	Capivasertib	09-Mar-19	Skipped
2	1	Durvalumab	29-Mar-19	10-Apr-19
	2	Capivasertib	11-Apr-19	11-Apr-19

The duration of an interruption is calculated differently for the final doses of a cycle that are missed compared to those that are missed during the cycle. The date of next dose is not used in the calculation for final doses of a cycle because it would be impacted if there was a delay to the next cycle starting. Therefore, the method above avoids double-counting the delay as both a delay and as part of an interruption.

If the last dose of a cycle is skipped and there is a delay to the start of the following cycle, the duration of the interruption is the time up to the day the dose was planned to be given in the next cycle (if there were no delays). The time between the planned cycle start day and actual cycle start day is included in the duration of delay calculation.

Note that total duration of dose interruptions of paclitaxel is not calculated.

8.3.4 Dose reduction

A dose reduction occurs when a dose is intentionally permanently reduced. This term is not used for interruptions or invalidly administered doses and it does not include instances where a subject's weight drops below a threshold leading to weight-based dosing. A dose reduction is counted once for each time the dose is reduced.

The reasons for delays, interruptions and reductions are not mutually exclusive for subjects with multiple events but they will only be counted once per category.

8.3.5 Duration of treatment exposure

8.3.5.1 Intended treatment duration – example

Durvalumab:

Date of first dose = 01-Mar-19, Date of death = N/A (subject still alive), Date of DCO = 20-Aug-19, Date of last non-zero dose = 08-May-19.

Hence A = 01-Mar-19, B = 08-May-19 + C, where C = 27, so B = 04-Jun-19

Intended treatment duration for durvalumab (days) = 04-Jun-19 – 01-Mar-19 + 1 = 96 days

Cycle	Day	Drug	Planned date	Actual date

1	1	Durvalumab	01-Mar-19	01-Mar-19
		Oleclumab	01-Mar-19	03-Mar-19
	15	Oleclumab	15-Mar-19	18-Mar-19
2	1	Durvalumab	29-Mar-19	10-Apr-19
		Oleclumab	10-Apr-19	10-Apr-19
	15	Oleclumab	24-Apr-19	Skipped
3	1	Durvalumab	08-May-19	08-May-19
		Oleclumab	08-May-19	09-May-19

8.3.5.2 Actual treatment duration – example

Using the example above,

Actual treatment duration for durvalumab (days) = 96 – 12 = 84 days.

8.3.6 Dose intake

For infusion administered drugs, a subject is considered to have received a dose if they receive >0 infusion volume. Only doses >0 are included in the calculation for calculated average dose intake. For orally-administered drugs, the exact dose received can be calculated.

8.3.6.1 RDI - example

Durvalumab planned 1500mg per cycle. When the full dose has not been administered, the actual dose intake would be calculated using the “actual dose intake” formulae at the start of this Section.

Cycle	Date	Duration (days)	Delay (days)	No. cycles, based on duration + delays (A)	No. actual cycles received (B)	Planned total dose D = Max(int(A), B)*1500mg	Actual dose intake d
1	01-Jan-19	28	+ 14				1500
2	12-Feb-19	28	+ 14				1000
3	26-Mar-19	28	+ 0				1500
4	23-Apr-19	28	+ 0				1200
Total		140		5	4	5*1500 = 7500mg	5200mg

In the above example,

RDI of durvalumab: d = 5200mg, D= 7500mg. RDI= 100%*(5200/7500) = 69.3%.

8.3.6.2 Calculated average dose intake – example

Calculated average dose intake per subject [mg] = average over all cycles[(sum[(actual dose intake [mg]/planned dose [mg]) for all doses in the cycle]/number of doses subject received per cycle)*100], where actual dose intake is calculated using the formulae at the start of this Section. Note that zero doses of infusion-administered drugs are not included in the calculation.

Oleclumab planned 3000mg on D1 and D15 of cycles 1 and 2, and D1 of cycles 3+. Subject had a planned dose reduction to 1500mg from C3D1.

Cycle	Day	Planned date	Actual date	Actual dose intake (mg)
1	1	01-Mar-19	03-Mar-19	3000
	15	15-Mar-19	18-Mar-19	2500
2	1	10-Apr-19	10-Apr-19	2000
	15	24-Apr-19	Skipped	0
3	1	08-May-19	09-May-19	1200

Average dose intake

$$= \text{Average of}\left(\left[\left(\frac{\frac{3000}{3000}+\frac{2500}{3000}}{2}\right)\times 100\%\right]+\left[\left(\frac{\frac{2000}{3000}+0}{1}\right)\times 100\%\right]+\left[\left(\frac{\frac{1200}{1500}}{1}\right)\times 100\%\right]\right)$$

$$= \frac{91.7\% + 66.7\% + 80\%}{3}$$

$$= 79.5\%$$