Ludwig Institute for Cancer Research (LICR)

STATISTICAL ANALYSIS PLAN

A Phase 1/2 Study of In Situ Vaccination with Tremelimumab and IV Durvalumab (MEDI4736) Plus the Toll-like Receptor Agonist PolyICLC in Subjects with Advanced, Measurable, Biopsy-accessible Cancers

Clinical Trial Protocol LUD2014-011

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LIST OF ABBREVIATIONS

Abbreviation	*Full Term*
AE	adverse event
ATC	Anatomical Therapeutic Class
BMI	body mass index
CI	confidence interval
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
IM	intramuscular
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
ITM	intratumoral
ITT	Intent-to-Treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ODCR	overall disease control rate
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PP	Per-Protocol
PR	partial response
PT	Preferred Term

RCD	recommended combination dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	System Organ Class
TEAE	treatment emergent adverse event
TLR	toll like receptor
TME	tumor microenvironment
TRAE	treatment-related treatment-emergent adverse event

1 INTRODUCTION

LUD2014-011 is an open-label, multicenter, Phase 1/2 study of the CTLA-4 antibody, tremelimumab, and the PD-L1 antibody, durvalumab (MEDI4736), in combination with the tumor microenvironment (TME) modulator polyICLC, a TLR3 agonist, in subjects with advanced, measurable, biopsy-accessible cancers.

The statistical analysis plan (SAP) contains a detailed description of the data presentations and statistical analyses that will be included in the clinical study report for Protocol LUD2014-011. The statistical methods and analyses described here are based on those presented in the study protocol (Amendment 5.1 dated 23July2019).

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

For Phase 1, the primary objective is to determine the recommended combination dose (RCD) of the dosing regimen, based on assessment of toxicity and tolerability. The secondary objective is to obtain preliminary evidence of clinical efficacy as measured by objective response rate (ORR) by Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) and Response Evaluation Criteria In Solid Tumors (RECIST) 1.1, progression-free survival (PFS), and overall survival (OS).

For Phase 2, the primary objective is the evaluation of clinical efficacy as measured by ORR, PFS, and OS.

For all Phase 1 and 2 cohorts, safety and tolerability will be evaluated based on adverse events, laboratory tests, vital sign measurements, and physical examinations. An exploratory objective is the evaluation of biological activity, including effects on the TME and immunological responses.

2.2 STUDY DESIGN

This is an open-label, multicenter, Phase 1/2 study to evaluate the CTLA-4 antibody, tremelimumab, and the PD-L1 antibody, durvalumab, in combination with the TME modulator polyICLC, a TLR3 agonist, in subjects with advanced, measurable, biopsy-accessible cancers. The study will be conducted at up to 8 sites in the US.

Subjects will receive intratumoral (ITM) and intramuscular (IM) administration of polyICLC and intravenous (IV) administration of durvalumab, together with either IV

or ITM administration of tremelimumab. The study will be conducted in 2 phases. There will be enrollment to 3 subject cohorts (1A, 1B, and 1C) in Phase 1.

Dose de-escalations for determination of the RCDs through the assessment of dose-limiting toxicities (DLTs) will be performed based on the available dose levels and respective standard 3 + 3 rules.

Once determined, the RCD of the dosing regimen will then be expanded in the Phase 2 portion of the study. If Cohort 1C is not cleared, the RCD of the previously cleared cohort will be used for Phase 2.

Subjects may receive study drug until withdrawn from treatment or the study per Protocol Section 3.1.10 or until the completion of Cycle 12. Treatment extension beyond 12 cycles is not planned.

2.2.1 Number of Subjects

Up to 102 subjects will be enrolled in the study.

Phase 1 will enroll up to 36 subjects to determine the RCDs of durvalumab or durvalumab and tremelimumab within each cohort (3-6 subjects per dose level for each of the 3 cohorts). Subjects in Phase 1 who are not fully evaluable for DLT, as defined in Protocol Section 3.1.11, will be replaced.

Phase 2 will evaluate up to 66 subjects treated with the RCDs of the dosing regimen. A total of (8 disease types)(6 subjects per disease type) = 48 subjects will be initially enrolled for the Phase 2 portion plus a potential additional (3 disease types)(6 subjects) = 18 subjects for three disease types having at least one response or stable disease for 24 weeks in the initial group (total of 48+18= 66 subjects).

2.2.2 Randomization Procedures

This is not a randomized study. For Phase 1 of the study, there will be enrollment to 3 subject cohorts, with staggered initiation of enrollment:

- Cohort 1A: IV Durvalumab + ITM/IM PolyICLC.
- Cohort 1B: IV Durvalumab + IV Tremelimumab + ITM/IM PolyICLC.
- Cohort 1C: IV Durvalumab + ITM Tremelimumab + ITM/IM PolyICLC.

After safety is demonstrated in the first 3-6 subjects in Cohort 1A, Cohorts 1B and 1C will open with alternating enrollment. Cohort 2 will expand the Phase 1 cohort treated at the RCD for Phase 2, and enrollment will occur without randomization.

The study will be under ongoing review by an internal data safety monitoring panel.

2.2.3 Efficacy Assessments

Tumor response disease assessments will be done in accordance with Table 1: Study Flowchart. The primary method for tumor response disease assessments will be by irRECIST, and the secondary method will be by RECIST 1.1 (see Protocol Section 8.5). Confirmation of response (CR/PR ≥ 4 weeks) is required for RECIST 1.1 and irRECIST. Confirmation of progression is recommended a minimum of 4 weeks after the first irPD assessment, when appropriate, per irRECIST.

Additionally, date of death or last follow-up will be recorded for each subject. Every effort will be made to follow subjects for overall survival after they discontinue the study.

2.2.4 Safety Assessments

Safety assessments include clinical laboratory tests, vital sign measurements, physical examinations, and subject interviews to detect new abnormalities and deteriorations of any pre-existing conditions and will be conducted according to Table 1: Study Flowchart.

Clinical laboratory tests will be conducted pre-dose and include:

- Hematology: CBC, differential, platelets
- Chemistry: glucose, BUN, creatinine, Na, K, Cl, CO2, Ca, Mg, protein, alb, Tbili, AST, ALT, ALP, LDH, Free T3, Free T4, TSH, Amylase, lipase
- Coagulation: PT, aPTT, INR
- Urinalysis
- Serum pregnancy test

Vital sign measurements include:

- Oral temperature
- Heart rate
- Respiratory rate
- Systolic and diastolic blood pressure

The investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as adverse events (AEs). All treatment-emergent, clinically significant abnormalities and deteriorations from the time of informed consent to the End of Study Visit will be recorded as AEs and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03.

2.2.5 Biological Activity Assessments

Tumor biopsies for TME assessments and blood samples for exploratory pharmacodynamic assessments will be collected as specified in Table 1: Study Flowchart. Additional biopsies may be obtained as appropriate.

[redacted]

2.2.6 Other Assessments

Medical history and demographics will be collected, and 12-lead electrocardiogram (ECG) and serum pregnancy test will be performed in accordance with Table 1: Study Flowchart.

Table 1. Study Flowchart

LUD 2014-011 Study Flowchart	Screening / Baseline (Day -21 to -1)	Treatment																				
		Cycle 1 (4 weeks)									Cycle 2 (4 weeks)								Cycle 3 (4 weeks)		Cycle 4 (4 weeks)	Cycle 5 (4 weeks)
Study Week		1			2		3		4		5		6		7		8		9		13	17
Cycle Day[1,2]		1±3	3±3	5±3	8±3	10±3	15±3	17±3	22±3	24±3	1±3	3±3	8±3	10±3	15±3	17±3	22±3	24±3	1±3	4±3	1±3	1±7
Study Day		1	3	5	8	10	15	17	22	24	29	31	36	38	43	45	50	52	57	60	85	113
Study Drug Administration																						
Durvalumab IV (all cohorts)		X									X								X		X	X
Tremelimumab IV (Cohort 1B only)		X									X								X		X	
Tremelimumab, intratumoral (Cohort 1C and Cohort 2 if 1C is cleared in Phase 1)		X			X		X				X				X				X		X	
Poly ICLC, Intratumoral[4]		X	X	X	X	X	X															
Poly ICLC IM								X	X	X	X	X	X	X	X	X	X	X	X	X		
Tumor and Disease Assessments																						
Disease Staging (date/stage at 1st diagnosis and at study entry)	X																					
Disease Assessment by irRECIST/RECIST1.1 (and imaging)[8]	X																				X	
Study Procedures and Examinations																						
Eligibility Assessment and Informed Consent (IC)[9]	X																					
Demographics (DoB, sex, height, race, ethnicity)	X																					
Physical Examination (incl. weight and ECOG PS)	X	X			X		X				X				X				X		X	X
Medical History	X																					
Vital Signs (T, HR, BP, RR)[10]	X	X	X	X	X	X	X	X			X				X				X		X	X
12- Lead ECG	X																					
Concomitant Medication (name, indication, dose, route, start & end dates) /Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (starting/worsening after IC)[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Specimens for Routine Laboratory Procedures																						
Blood Hematology (CBC, differential, platelets)[3]	Day -7 to -1	X			X		X				X				X				X		X	X
Chemistry (Glucose, BUN, creat, Na, K, Cl, CO2, Ca, Mg, protein, alb, Tbili, AST, ALT, ALP, LDH)[3]	Day -7 to -1	X			X		X				X				X				X		X	X
Chemistry cont: Free T3, Free T4, TSH[3]	Day -7 to -1	X			X		X				X				X				X		X	X
Chemistry cont: Amylase and lipase[3]	Day -7 to -1	X			X		X				X				X				X		X	X
Hemoglobin A1c	Day -7 to -1																					
Serum Pregnancy Test (urine only Day 1)[3]	Day -7 to -1	X									X								X			X
Coagulation (PT, aPTT, INR)[3]	Day -7 to -1	X			X		X				X				X				X		X	X
Urinalysis[3]	Day -7 to -1	X			X		X				X				X				X		X	X
Blood for Biological Markers																						
Circulating soluble factors (Antibody, Chemokines, Cytokines -serum)	X	X[3]			X[3]		X[3]				X[3]								X[3]		X[3]	
PBMCs (Flow cytometry, T-cell Responses and Circulating T-cells)	X	X[3]			X[3]		X[3]				X[3]								X[3]		X[3]	
RNA profiling (whole blood)	X				X[3]		X[3]				X[3]								X[3]		X[3]	
Other Procedures																						
Tumor Biopsy[5]	X						X[3]				X[3]											
Long-Term Follow-up																						
Overall Survival																						
Progression-free Survival[7]																						

LUD 2014-011 Study Flowchart (cont.)	Treatment							Visit for Subjects who Discontinue Treatment Prematurely	On Study Follow-up			Post Study Follow-up
	Cycle 6 (4 weeks)	Cycle 7 (4 weeks)	Cycle 8 (4 weeks)	Cycle 9 (4 weeks)	Cycle 10 (4 weeks)	Cycle 11 (4 weeks)	Cycle 12 (4 weeks)		Last Study Drug +28±3 days	Last Study Drug +56±3 days	Last Study Drug +91±7 days	Every 3 mos for 2 yrs after completion of treatment; then every 6 mos until 5 yrs from study entry; then yearly until 10 yrs from study entry
Study Week	21	25	29	33	37	41	45					
Cycle Day[1,2]	1±7	1±7	1±7	1±7	1±7	1±7	1±7					
Study Day	141	169	197	225	253	281	309					
Study Drug Administration												
Durvalumab IV (all cohorts)	X	X	X	X	X	X	X					
Tremelimumab IV (Cohort 1B only)												
Tremelimumab, intratumoral (Cohort 1C and Cohort 2 if 1C is cleared in Phase 1)												
Poly ICLC, Intratumoral[4]												
Poly ICLC IM												
Tumor and Disease Assessments												
Disease Staging (date/stage at 1st diagnosis and at study entry)												
Disease Assessment by irRECIST/RECIST1.1 (and imaging)[8]		X		X		X		X	X			
Study Procedures and Examinations												
Eligibility Assessment and Informed Consent (IC)[9]												
Demographics (DoB, sex, height, race, ethnicity)												
Physical Examination (incl. weight and ECOG PS)	X	X	X	X	X	X	X	X	X	X	X	
Medical History												
Vital Signs (T, HR, BP, RR)[10]	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG												
Concomitant Medication (name, indication, dose, route, start & end dates) /Procedures	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events (starting/worsening after IC)[6]	X	X	X	X	X	X	X	X	X	X	X	
Specimens for Routine Laboratory Procedures												
Blood Hematology (CBC, differential, platelets)[3]	X	X	X	X	X	X	X	X	X	X	X	
Chemistry (Glucose, BUN, creat, Na, K, Cl, CO2, Ca, Mg, protein, alb, Tbili, AST, ALT, ALP, LDH)[3]	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont: Free T3, Free T4, TSH[3]	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont: Amylase and lipase[3]	X	X	X	X	X	X	X	X	X	X	X	
Hemoglobin A1c												
Serum Pregnancy Test (urine only Day 1)[3]		X		X		X		X	X		X	
Coagulation (PT, aPTT, INR)[3]	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[3]	X	X	X	X	X	X	X	X	X	X	X	
Blood for Biological Markers												
Circulating soluble factors (Antibody, Chemokines, Cytokines -serum)		X[3]					X[3]	X	X[11]			
PBMCs (Flow cytometry, T-cell Responses and Circulating T-cells)		X[3]					X[3]	X	X[11]			
RNA profiling (whole blood)		X[3]					X[3]	X	X[11]			
Other Procedures												
Tumor Biopsy[5]								optional	optional			
Long-Term Follow-up												
Overall Survival												X
Progression-free Survival[7]												X

1. For each subject, there will be one allowed delay of up to one week for a scheduled visit; however, the delay can only occur after Cycle 1 is complete
2. Starting with Cycle 5, the intervals for visit days will change to ±7 days; however, a 3-week interval must maintained between durvalumab doses.
3. Collected pre-dose (prior to drug administration). It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.
4. For intratumoral polyICLC, a 7-day dosing window is permitted provided that all injections are administered within the first 21 days of Cycle 1; injections must be administered ≥ 24 hours apart
5. Also conducted at time of progression and end of treatment; injected and uninjected tumors on Day 15 and Cycle 2 Day 1, and from the same lesion each time if possible. See Sections 4.3.1.1 and 5.1 (#2) for details on biopsies. Note: the Screening/Baseline biopsy may be done on the Cycle 1/Day 1 Visit as long as it is done prior to start of any treatment.
6. See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.
7. For subjects who did not experience progression while on study
8. Subsequent imaging at 4 to 8 weeks after first documentation of irRECIST-defined progression must be performed.
9. Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart
10. See Section 6.5 for assessment before/during/after IV infusions; Section 6.1.3.1 for intratumoral tremelimumab vitals assessments; Section 6.3.3 for intratumoral and IM polyICLC vitals assessments.
11. There is no need to repeat these assessments if they were done at the Premature Discontinuation Visit or at the last on treatment visit.

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher for Windows.

3.1.2 Presentation of Data Summaries

Unless otherwise specified, tables for Phase 2 subjects will be presented by specific disease type (which may include Head and Neck Squamous Cell Carcinoma, Locally Recurrent Breast Cancer, Sarcoma, Merkel Cell Carcinoma, Cutaneous T-cell Lymphoma, Metastatic Melanoma, Genitourinary Cancers with Accessible Metastases, or any solid tumors with masses that are accessible) within analysis population. Only disease types for which at least one subject was enrolled will be presented. An "All Subjects" column will be included as appropriate. When Phase 1 is presented as a separate table, "All Subjects" will include total for Phase 1 only. When Phase 2 is presented, this column will include the total for all subjects in Phase 1 + all subjects in Phase 2 and will be labeled "All Subjects (Phase 1/Phase 2). This will also be footnoted.

Subjects from Cohort 1C who are treated at the RCD will be included in expansion; thus, the subjects in the Phase 1 cohort treated at the RCD will be included in both the Phase 1 and Phase 2 tables.

All clinical study data will be presented in subject data listings.

3.1.3 Reporting of Numerical Values

Relevant descriptive statistics (n, mean, standard deviation, 25th percentile, median, 75th percentile, minimum, and maximum) will be calculated for continuous variables. Confidence intervals (CIs) will be provided where appropriate.

Frequencies and percentages will be presented for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage.

Means, medians, and confidence intervals will be reported to one decimal place more than the data reported on the case report form (CRF) or by the laboratory/vendor. Standard deviations will be reported to two decimal places more than the data

reported. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the laboratory/vendor.

3.1.4 Baseline Value and Change from Baseline

Baseline value is defined as the most recent non-missing value obtained prior to administration of first dose of study treatment. Change from baseline will be calculated by subtracting the baseline value from the relevant post-baseline assessment for each subject (i.e., post-baseline – baseline).

3.1.5 Pre-Dose Value and Change from Pre-Dose

Pre-dose value is defined as the last non-missing value obtained prior to dosing at a particular visit. Change from pre-dose will be calculated by subtracting the pre-dose value from the post-dose assessment for each subject at the visit (i.e., post-dose – pre-dose).

3.1.6 Handling of Missing/Incomplete Values

Unless otherwise explicitly specified, missing data will not be imputed; observed cases will be used in the analyses.

3.1.7 Handling of Repeated Assessments

If multiple results are available for a post-dose assessment at the same scheduled time point, then the earliest result recorded for that time point will be used in all descriptive summaries. All results will be displayed in subject data listings, and abnormal values will be flagged, where applicable.

3.1.8 Handling of Missing/Incomplete Date/Time

All analyses of AEs will be based on the principle of treatment emergence. An AE is considered to be treatment emergent if it has a start date/time on or after the date/time of first dose of study treatment; if the AE is missing start time, it is considered to be treatment emergent if it has a start date on or after the date of first dose of study treatment. For missing or incomplete AE start date, the following criteria will be used to determine whether an AE is treatment emergent:

Missing AE start day:

- If the partial date contains a different month from the date of first study dose, then impute it as the first day of the month.
- If it contains the same month as the date of first dose, then impute it as date of first dose.

Missing AE start day and month:

- If the partial date contains a different year from the date of first dose, then impute the missing day and month as Dec 31.
- If it contains the same year as the date of first dose, then impute the missing day and month as day and month of first dose.

Completely missing AE date:

- Impute the missing date as the date of first dose.

A medication or procedure is considered to be concomitant if it has a start or end date on or after the date of first dose of study treatment and on or before the last day of On Study Follow-Up. In order to determine whether a medication or procedure with an incomplete or missing start or end date is concomitant, the following criteria will be used:

- If both the start and stop dates of a particular medication are missing, that medication will be considered concomitant.
- If the start date of a medication is missing and the stop date of that medication falls on or after the first dose date, that medication will be considered concomitant.
- If the start date of a medication is missing and the stop date of the medication is prior to the first dose date, that medication is considered *not* concomitant.
- If the start date of a medication is prior to the first dose date and the stop date of the medication is missing, that medication is considered concomitant.

3.2 Analysis Populations and Subgroups

3.2.1 Intent-to-Treat Population

The Intent-To-Treat (ITT) Population and the Safety Population are the same for this study and are defined as all subjects who receive at least one dose of tremelimumab, durvalumab, or polyICLC. All tables, listings, and figures will identify this group of subjects as the ITT Population.

3.2.2 Per-Protocol Population for DLT Assessment in Phase 1

The Per-Protocol Population for DLT Assessment includes subjects in Cohorts 1A through 1C who fulfill the criteria below.

(1) All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Protocol Section 3.1.9).

(2) All subjects with no DLT who receive at least 75% of the total dose of each study drug and undergo respective safety assessments, without major protocol violations, over the entire DLT evaluation period.

Subjects who fulfill the criteria will be identified by the Sponsor.

3.2.3 Per-Protocol Population for Phase 2 Clinical Efficacy

Subjects in the Phase 1 cohort treated at the RCD and in Phase 2 who receive the minimum required dose of each study drug and undergo appropriate disease assessments (radiological or clinical), without major protocol violations that could impact assessments of efficacy, are considered fully evaluable and will be included in the Per-Protocol (PP) Analysis Population. The minimum required dose of each study drug that a subject must receive to be fully evaluable is:

- 2 durvalumab infusions (including partial infusions over 50%)
- 3 of 5 tremelimumab administrations
- 10 of 14 polyICLC administrations (regardless of route)

The Sponsor will provide a list of the subjects who meet the above criteria, which will be cross-checked with the treatment exposure data collected on the CRF. Subjects in Phase 2 who do not meet these requirements may be replaced. The PP Population will be used for analysis of clinical efficacy, in addition to the ITT Population. Subjects will be analyzed by disease type.

3.3 Analysis Variables

3.3.1 Efficacy Variables

The evaluation of clinical efficacy is the primary objective of Phase 2 and the secondary objective of Phase 1. Clinical efficacy will be determined by tumor response, PFS, and OS, using irRECIST as the primary method and RECIST 1.1 as the secondary method (see Protocol Section 8.5).

Subsequent imaging at a minimum of 4 weeks after first documentation of progression is recommended as per irRECIST.

If there is clinical progression or progressive disease resulting in the subject discontinuing treatment (defined as the last dose date occurring no more than 7 days after the date of progression), confirmation of progression would not be expected.

Confirmation is also not expected for progressions identified in the post-study follow-up period.

Post-study follow-up visits collect the investigator's assessment of disease progression via both irRECIST and RECIST. A post-study assessment of "No Progressive Disease" will assume that subject's previous irRECIST/RECIST assessment remains in effect. A post-study assessment of "Progressive Disease Not Previously Reported" will be considered as a confirmed Disease Progression. Appendices 5.1-5.2 contain the general algorithms for confirming response using irRECIST and RECIST 1.1.

3.3.1.1 Objective Response Rate

ORR is defined as the percentage of evaluable subjects meeting criteria of complete response (CR) or partial response (PR), confirmed at a subsequent time point (≥ 4 weeks). In calculating ORR, subjects who drop out prior to meeting the responder criteria will be considered as non-responders. Tumors injected and/or biopsied during the study will not be considered measurable for ORR but will be assessed as non-measureable lesions to the extent that marked progression of a non-measurable lesion is inconsistent with an objective response.

3.3.1.2 Overall Disease Control Rate

Overall Disease Control Rate (ODCR) is defined as the percentage of subjects who have stable disease (SD) for at least 6 months, or PR or CR over a period of at least 4 weeks. In calculating ODCR, subjects who drop out prior to meeting the responder criteria will be considered as non-responders.

3.3.1.3 Progression-Free Survival Time

PFS will be defined as the number of days from the date of first dose of study drug to the date of earliest disease progression based on irRECIST, clinical progression or to the date of death, if disease progression does not occur. PFS based on RECIST 1.1 will also be presented but will not be the primary method. If a subject does not experience progression or death by the last on study follow-up or is lost to follow-up, then the subject will be censored at the date of the last adequate tumor assessment. One exception to this is a subject who completes the study or discontinues the study for reasons other than progression (e.g., AE) and did not receive any alternate anti-cancer treatment. In these cases, the post study follow-up visits will be examined for disease assessments until progression is noted. If progression is not noted, then the subject will be censored at the date of the last "No Progressive Disease" assessment in the post study follow-up, using the same criteria (RECIST 1.1, irRECIST, or "Unequivocal Clinical Progression", as applicable). See Section 3.8.2 for additional details. Subjects with no relevant tumor response assessment will be censored at the start of treatment. Appendix 5.3 contains complete details regarding censoring for PFS.

3.3.1.4 Overall Survival Time

OS time will be based on data collected during the study and Post Study Follow-Up and is defined as the number of days from the date of first dose until the recorded date of death due to any cause, or last follow-up. Subjects who are still alive and subjects lost to follow-up will be censored on the date when they were last known to be alive. Every effort will be made to follow subjects for OS after they complete or discontinue the study.

3.3.2 Safety Variables

The evaluation of safety and tolerability is a secondary objective for all cohorts. Safety variables include clinical laboratory results, vital signs, physical examinations, and AEs. Clinically significant abnormalities on the ECG or noted during the physical examination are reported as AEs on the CRF.

3.3.2.1 Adverse Events

All AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 19.0 and will be classified by MedDRA System Organ Class (SOC) and Preferred Term (PT). Analyses of AEs will be based on the principle of treatment emergence. An AE is considered to be treatment-emergent if it has a start date/time on or after the date/time of first dose of study drug. Please reference Section 3.1.8 for the handling of partial date/time in determining treatment emergence.

3.3.2.2 Clinical Laboratory Evaluations

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Change and shift in chemistry, hematology, and coagulation parameters from baseline to relevant time points will be calculated.

Clinical laboratory tests include:

- Hematology: WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, RBC, Hemoglobin, Hematocrit, Platelets
- Chemistry: glucose, BUN, creatinine, Na, K, Cl, CO2, Ca, Mg, protein, alb, Tbili, AST, ALT, ALP, LDH, Free T3, Free T4, TSH, Amylase, lipase
- Coagulation: PT, aPTT, INR
- Urinalysis
- Serum pregnancy test

3.3.2.3 Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and oral temperature. Change from baseline to relevant time points will be calculated.

3.3.3 Biological Activity Variables

The exploratory objective for all cohorts is to evaluate biological activity. Biological activity variables will be analyzed by another entity and are not included in the analysis sections below.

3.4 Subject Disposition and Evaluability

3.4.1 Subject Disposition

Subject disposition will be summarized by cohort and overall in Phase 1, by disease type in Phase 2 (including the Phase 1 cohort treated at the RCD), and overall (all subjects). The number of subjects enrolled, and the numbers and percentages of subjects in the ITT Population and the relevant PP Populations will be presented. The numbers and percentages of Phase 1 subjects evaluable for DLT, experiencing a DLT, completing and not completing treatment and the reasons for treatment discontinuation, and completing and not completing the study (including the 90 day On Study Follow-Up period) and reasons for study discontinuation will also be summarized. All percentages will be based on the number of subjects in the ITT Population.

All subject disposition data will be presented in listings. Subject disposition during Post Study Follow-Up will also be listed.

3.4.2 Protocol Deviations

All protocol deviations will be shown in a subject listing. Protocol deviations that exclude Phase 1 subjects treated at the RCD or Cohort 2 subjects from the PP Population will be flagged.

3.5 Demographics and Baseline Characteristics

Summaries of subject demographics and baseline characteristics will be provided for Phase 1 by cohort (and total for Phase 1), for Phase 2 by disease type (including the Phase 1 cohort treated at the RCD), and overall for all subjects in the ITT Population for Phase 1 and Phase 2 combined.

3.5.1 Demographics and Baseline Characteristics

Descriptive statistics will be provided for age (years), height (cm), weight (kg), and body mass index [BMI (kg/m^2)]. Frequencies and percentages will be tabulated for sex, primary race, and ethnicity.

Demographics will be presented in a subject listing.

3.5.2 Baseline Disease Characteristics

Frequencies and percentages will be presented for Eastern Cooperative Oncology Group (ECOG) performance status, TNM(B) classification, tumor staging at initial diagnosis, tumor staging at study entry, and whether a subject had prior oncological treatment, radiation, and surgery.

Baseline disease characteristics will be presented in a subject listing.

3.5.3 Non-Oncological Medical History

Medical history will be coded by body system and preferred term using MedDRA Version 19.0. Frequency and percentage of subjects having a non-oncological medical condition in each body system will be summarized for Phase 2 by disease type (including the Phase 1 cohort treated at the RCD) and overall for all subjects in the ITT population combined.

Non-oncological medical history will be presented in a subject listing.

3.5.4 Oncological Medical History

Prior cancers not under study, oncological treatment, radiation, and surgical history will be presented in subject listings.

3.6 Prior and Concomitant Medications/Procedures

A concomitant medication is defined as any drug or substance administered between the date of the first dose of study treatment and the last day of On Study Follow-Up. This includes medications that were started prior to screening, if their use continued during or after dosing. Similarly, a concomitant procedure is any medical procedure/surgery undergone between the date of the first dose of study treatment and the last day of On Study Follow-Up. Refer to Section 3.1.8 for the handling of incomplete/partial dates in determining whether a medication or procedure is concomitant.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (Version March 2016) and classified by Anatomical Therapeutic Class

(ATC) Level 4 and PT. Frequencies and percentages of subjects using each concomitant medication will be presented for Phase 2 by disease type (including the Phase 1 cohort treated at the RCD) and overall for all subjects in the ITT population combined. The summary will be sorted alphabetically by ATC level 4 term, and within ATC level 4 term, by decreasing PT frequency for all subjects.

Concomitant procedures/surgeries will be coded based on MedDRA Version 19.0 using SOC and PT. All prior and concomitant medications and procedures/surgeries will be presented in subject listings.

3.7 Treatment Exposure

Descriptive statistics will be displayed for treatment duration (weeks), total number of cycles treated, total number of doses received, and cumulative dose of each study treatment [Durvalumab (MEDI4736), PolyICLC, Tremelimumab (IV), and Tremelimumab (ITM)] for Phase 1 by cohort (and total for Phase 1), for Phase 2 by disease type (including the Phase 1 cohort treated at the RCD), and overall for all subjects in the ITT Population for Phase 1 and Phase 2 combined. Treatment duration will be calculated as follows: [(date of last dose of any study drug – date of first dose of any study drug + 1)/7]. Subjects will be counted as treated for a cycle if they received any study drug during that cycle.

All treatment exposure data will be presented in subject listings.

3.8 Efficacy Analysis

Each analysis of clinical efficacy (tumor response, PFS, and OS) will be performed as indicated within each population:

- Cohorts 1A-1C, ITT Population – by cohort and overall
- Phase 1 cohort treated at the RCD + Cohort 2, ITT Population – by disease type
- Phase 1 cohort treated at the RCD + Cohort 2, PP Population – by disease type

Efficacy analysis variables are defined in Section 3.3.

3.8.1 Tumor Response

ORR is defined as the percentage of evaluable subjects meeting criteria of CR or PR, confirmed at a subsequent time point (≥ 4 weeks). ODCR is defined as the percentage of subjects who have SD for at least 6 months, or PR or CR over a period of at least 4 weeks.

The ORR, ODCR, and number and percentage of subjects meeting the best overall response criteria of CR, PR, SD, and PD based on irRECIST and RECIST 1.1 will be displayed, as well as the number and percentage of subjects not evaluable or with missing response. Subjects who had no disease assessment based on irRECIST or RECIST 1.1 but had clinical progression will be considered as having a best response of PD.

For disease types accruing 6+6=12 subjects, an exact 90% CI for ORR will be computed. In calculating ORR and ODCR, subjects who drop out prior to meeting the responder criteria will be considered as non-responders. For responders, descriptive statistics (n, median, minimum, and maximum) will be presented for duration of response, defined as the time from the first response of PR or CR to the date of disease progression or death.

All irRECIST and RECIST 1.1 target lesions, non-target lesions, tumor response, and new lesions will be presented in subject listings.

3.8.2 Progression-Free Survival

PFS is defined as the number of days from the date of first dose of study drug to the date of earliest disease progression based on irRECIST or clinical progression, or to the date of death, if disease progression does not occur during treatment and/or on-study follow-up. PFS based on RECIST 1.1 will also be presented but will not be the primary method. Appendix 5.3 contains complete details regarding censoring for PFS.

Tumor response progressions reported during the post-study follow-up period will be included in the derivation of PFS if:

(1) The frequency of the tumor assessment was performed according to standard of care and preferably using irRECIST and/or RECIST 1.1 or was "Unequivocal Clinical Progression", with the method recorded in the eCRF; and
(2) The subject a) did not start any alternative anti-cancer therapy; b) did not have any prior follow-up visits which were missing or where disease progression status was 'Unknown' (the sponsor will manually review and confirm these cases), and c) was not lost to follow-up during the post-study follow-up period.

Progressions based on irRECIST require confirmation at a subsequent assessment at least 4 weeks after the first documentation of progression (exceptions for clinical progressions and post-study follow-up progressions, as described in Section 3.3.1). When confirmation is required, the date of progression is the date of the first documentation of progression.

The number and percentage of subjects who experienced disease progression, died without progression, survived without progression, discontinued from treatment or the study, initiated alternate therapy, progressed or died following two or more missed tumor assessments, were lost to follow-up (unknown survival and/or progression status), and are missing baseline or post-baseline tumor response assessments will be presented. Subjects are considered as having baseline tumor assessments if they have at least one target lesion at baseline. Descriptive statistics (minimum, maximum, 25th percentile, median, 75th percentile, and the corresponding 95% CIs) will be presented for PFS time using the Kaplan-Meier method.

Additionally, the Kaplan-Meier PFS curve will be displayed graphically by disease type using both irRECIST and RECIST 1.1 response criteria.

3.8.3 Overall Survival

OS time is defined as the number of days from the date of first dose until the recorded date of death due to any cause, or last follow-up.

The number and percentage of subjects who died, survived, and were lost to follow-up at the end of the study will be presented. Subjects who are still alive or who were lost to follow-up will be censored on the date when they were last known to be alive. Descriptive statistics (minimum, maximum, 25th percentile, median, and 75th percentile, and the corresponding 95% CIs) will be presented for OS time using the Kaplan-Meier method. Median duration of follow-up and the 95% CI for the median will be calculated using a reverse Kaplan-Meier analysis.

Additionally, the Kaplan-Meier OS curve will be displayed graphically by disease type.

3.9 Safety Analysis

All safety analyses will be performed using the ITT Population and presented by Phase 2 disease type (including the Phase 1 cohort treated at the RCD) and overall (all subjects in Phase 1 and Phase 2 combined), unless otherwise indicated.

3.9.1 Adverse Events

All adverse events will be coded using MedDRA Version 19.0 and will be classified by MedDRA SOC and PT.

Analyses of AEs will be based on the principle of treatment emergence. A treatment-emergent AE (TEAE) is an AE occurring or worsening in severity on or after the date/time of first dose of study drug. Please reference Section 3.1.8 for the handling of partial date/time in determining treatment emergence.

For the presentation of AE incidences, the SOCs will be sorted alphabetically, and within SOC, the PTs will be presented by decreasing frequency in all subjects and then alphabetically. Summaries by PT alone will be presented by decreasing frequency in all subjects and then alphabetically. If a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject. Similarly, if a subject has more than one PT within the same SOC, the subject will be counted only once in that SOC. AE summaries will be presented for Phase 2 by disease type (including the Phase 1 cohort treated at the RCD) and overall for all subjects (Phase 1 + Phase 2) in the ITT population.

All AEs, TEAEs, treatment-related TEAEs (TRAEs), TEAEs leading to study treatment discontinuation, serious adverse events (SAEs), DLTs, and deaths will be displayed in subject listings.

3.9.1.1 Summary of TEAEs

The numbers and percentages of subjects who experienced any TEAE, treatment-related TEAEs (TRAEs), DLTs, TEAE with Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher, TRAE with CTCAE grade 3 or higher, SAEs, treatment-related SAEs, TEAEs leading to treatment discontinuation, and death will be presented. TRAE is defined as a TEAE with a relationship to any study treatment (tremelimumab, durvalumab, or PolyICLC) of “Possibly Related”, “Probably Related”, or “Definitely Related”. This summary will also be displayed for Phase 1 by cohort and overall within Phase 1.

3.9.1.2 Incidence of TEAEs

The number and percentage of subjects who experienced any TEAE as well as the number and percentage of subjects who experienced any TEAE within each specific

SOC and PT will be presented. A summary table of TEAEs by PT will also be presented.

3.9.1.3 TEAEs by Maximum CTCAE Grade

The incidence of TEAEs will be presented by maximum CTCAE grade for each SOC and PT. If a subject experiences more than one occurrence of the same PT, the subject will be counted only once under the maximum severity grade at which it was experienced. TEAEs with missing severity will be classified as missing.

3.9.1.4 Treatment-Related TEAEs

TEAEs with a relationship to any study treatment (tremelimumab, durvalumab, or PolyICLC) of "Possibly Related", "Probably Related", or "Definitely Related" will be classified as treatment-related and presented by SOC and PT. TEAEs with missing relationship will be classified as treatment-related. Additionally, TRAEs should be broken out by relationship to each individual study drug.

3.9.1.5 Treatment-Related TEAEs by Maximum CTCAE Grade

The incidence of TRAEs will be presented by maximum CTCAE grade for each SOC and PT. If a subject experiences more than one occurrence of the same PT, the subject will be counted only once under the maximum severity grade at which it was experienced. TRAEs with missing severity will be classified as missing.

3.9.1.6 CTCAE Grade ≥ 3 TEAEs

The incidence of TEAEs with CTCAE grade ≥ 3 will be presented by SOC and PT.

3.9.1.7 CTCAE Grade ≥ 3 TRAEs

The incidence of TRAEs with CTCAE grade ≥ 3 will be presented by SOC and PT.

3.9.1.8 Serious Adverse Events

The incidence of SAEs will be summarized by SOC and PT.

3.9.2 Clinical Laboratory Evaluation

The clinical laboratory parameters that will be collected are listed in Section 3.3.2.2 and will be analyzed using the ITT Population, for Phase 2 by disease type (including the Phase 1 cohort treated at the RCD), and overall (all subjects in Phase 1 and Phase 2 combined).

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. For hematology, coagulation, and

chemistry parameters, frequencies and percentages will be presented for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. Additionally, for each continuous hematology, coagulation, and chemistry parameter, descriptive statistics will be presented for the observed value and change from baseline at each post-baseline assessment time point.

All clinical laboratory values will be presented in subject listings. Out of normal range values will be flagged.

3.9.3 Vital Signs

Oral temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate will be measured at baseline and at select time points before, during, and after tremelimumab and durvalumab infusions, according to Protocol Section 6.5. Vital signs before, during, and after durvalumab infusions and tremelimumab infusions will be analyzed for all subjects combined in the ITT Population.

Descriptive statistics will be presented for the observed value and change from pre-dose assessment in the first four cycles. Line plots of mean ± standard error over time will be displayed for the first four cycles.

All vital sign data will be presented in a subject data listing.

3.9.4 ECG

Clinically significant ECG abnormalities are reported as AEs on the CRF.

3.9.5 Physical Examination

Clinically significant abnormalities noted during the physical examination are reported as AEs on the CRF.

3.10 Biological Activity Analysis

The analysis of biological activity data will be performed by a separate entity and will be described in a separate document.

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Figure 14.2.2.3	Kaplan Meier Estimate of Progression-Free Survival (PFS) Based on irRECIST – Cohort 1C and Expansion Phase – Per-Protocol Population for Phase 2 Clinical Efficacy
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5 Appendix

5.1 Confirmation of Response in irRECIST

The following table displays the general algorithm for confirming response using irRECIST. Confirmation of more complex cases, such as a NE from an unscheduled visit between two irCRs, will be programmed appropriately.

Overall Response First Time Point	Overall Response Subsequent Time Point (at least 4 weeks apart)	Visit Response at First Time Point
irCR	irCR	irCR
irCR	irPR	irSD, irPD, or irPR
irCR	irSD	irSD provided minimum criteria for irSD duration are met at the first time point. Otherwise irPD
irCR	irPD	irSD provided minimum criteria for irSD duration are met at the first time point. Otherwise irPD
irCR	NE	irSD provided minimum criteria for irSD duration are met at the first time point. Otherwise NE
irPR	irCR	irPR
irPR	irPR	irPR
irPR	irSD	irSD
irPR	irPD	irSD provided minimum criteria for irSD duration are met at the first time point. Otherwise irPD
irPR	NE	irSD provided minimum criteria for irSD duration are met at the first time point. Otherwise NE
NE	NE	NE

Abbreviations: CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Estimable

In addition, irPD is recommended to be confirmed as appropriate by consecutive assessment ≥4 weeks after the first documentation. If there is clinical progression or progressive disease resulting in the subject discontinuing treatment (defined as the last dose date occurring no more than 7 days after the date of progression), confirmation of progression would not be expected. Confirmation is also not expected for progressions identified in the post-study follow-up period. In the case of irSD,

measurements must have met the irSD criteria at least once after the first dose of study treatment.

5.2 Confirmation of Response in RECIST 1.1

The following table displays the general algorithm for confirming response using RECIST 1.1. Confirmation of more complex cases, such as a NE from an unscheduled visit between two CRs, will be programmed appropriately.

Overall Response First Time Point	Overall Response Subsequent Time Point	Visit Response at First Time Point
CR	CR	CR
CR	PR	SD, PD, or PR
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD
PR	NE	SD
NE	NE	NE

Abbreviations: CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Estimable

*In the case of SD, measurements must have met the SD criteria at least once after the first dose of study treatment.

5.3 Censoring Rules for PFS

The following censoring rules aim to follow the Food and Drug Administration guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics and will be used for PFS analysis.

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Date of first dose	Censored
No post-baseline tumor assessments, in the absence of documented progression or death	Date of first dose	Censored
Documented Progression	Earliest date of progression	Event
No progression	Date of last scan*	Censored
Treatment or study discontinuation	Date of last scan*	Censored
Lost to follow-up without documented progression	Date of last scan*	Censored
New anticancer treatment started	Date of last scan* prior to new anticancer treatment started	Censored
Death without documented progression and is not after two or more missed tumor assessment visits	Date of death	Event
Death or progression after two or more missed tumor assessment visits	Date of last scan*	Censored

[source: https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf]

*Scheduled or unscheduled visit with a disease assessment of [irCR, irPR, irSD, or unconfirmed irPD (for irRECIST)] or [CR, PR, or SD (for RECIST 1.1)].

As subjects may have more than one criteria apply for censoring, the following hierarchy will implemented:

(1) If the subject had no baseline tumor assessment, censor at date of first dose.
(2) Otherwise, if the subject started a new anti-cancer therapy (prior to progression), censor at the date of the last adequate tumor assessment on or prior to the new therapy.
(3) Otherwise, if the subject had progression:
    a) If the subject missed two or more tumor assessments prior to progression, censor at the later of the date of first dose and the date of the last adequate tumor assessment prior to the first missed assessment.†
    b) Otherwise count as an event.

(4) Otherwise, if the subject died:
   a) If the subject had no post-baseline disease assessment and the death date occurred after study day 88 (first scheduled assessment on Day 85 + 3 day window), censor at date of first dose.
   b) Otherwise, if the subject missed two or more tumor assessments prior to death, censor at the later of the date of first dose and the date of the last adequate tumor assessment prior to the first missed assessment.†
   c) Otherwise, count as an event.
(5) Otherwise, if the subject discontinued treatment or study, censor at the later of date of first dose and the date of the last adequate tumor assessment.
(6) Otherwise, if the subject had no post-baseline tumor assessment and was on study after study day 88 (first scheduled assessment on Day 85 + 3 day window), censor at date of first dose.
(7) Otherwise, if the subject was lost to follow-up, censor at the later of the date of first dose and the date of the last adequate tumor assessment.
(8) Otherwise, if the subject is ongoing, censor at the later of the date of first dose and the date of the last adequate tumor assessment.

†The occurrence of two or more missed tumor assessments is not expected on study and will be identified by LICR should it occur.