Ludwig Institute for Cancer Research (LICR)

STATISTICAL ANALYSIS PLAN

Phase 1/2 Study of Chemo-immunotherapy with Toll-like Receptor 8 Agonist Motolimod (VTX-2337) and anti-PD-L1 Antibody MEDI4736 in Subjects with Recurrent, Platinum-Resistant Ovarian Cancer for Whom Pegylated Liposomal Doxorubicin (PLD) is Indicated

Clinical Trial Protocol LUD2014-001
NCT02431559

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SIGNATURE PAGE

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DOCUMENT HISTORY

Version	Author	Description
1.0	[redacted]	New Document
2.0	[redacted]	• (Section 2.2.4 and 3.9.2) Removed reference to CTCAE grades for laboratory data. • (3.1.5) Added detail regarding handling of repeated assessments on scheduled time points post-treatment. • (3.3.2) Added definition of TEAE and TRAE. • (3.3.1) Updated list of demographic data included. • (3.9) Updated with additional detail regarding adverse event reporting. • (3.9.3) Added detail regarding pre-dose and end of infusion records to include in analysis of change in vital signs. • (3.9.5 and 3.9.6) Updated derivation of percentages to be based on subjects with non-missing data for both baseline and corresponding post-treatment time point.

LIST OF ABBREVIATIONS

Abbreviation	*Full Term*
AE	Adverse Event
ATC	Anatomical Therapeutic Class
BRCA	Breast Cancer susceptibility gene
CA-125	Cancer Antigen 125
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
ITT	Intent to Treat
irPD	Immune Response Progressive Disease
MDSC	Myeloid Derived Suppressor Cell
MedDRA	Medical Dictionary of Regulatory Activities
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ODCR	Overall Disease Control Rate
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells

Abbreviation	*Full Term*
PD	Progressive Disease
PFS	Progression-free Survival
PLD	Pegylated Liposomal Doxorubicin
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
Q4W	every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TRAE	Treatment Related Adverse Event
WHO	World Health Organization

1 INTRODUCTION

LUD2014-001 is an open-label, non-randomized, multicenter Phase 1/2 study of motolimod and MEDI4736 in subjects with recurrent, platinum-resistant ovarian cancer, scheduled to receive pegylated liposomal doxorubicin (PLD). The clinical efficacy and safety of the study drugs in combination will be evaluated during this clinical trial.

Per Amendment 2, motolimod dosing was discontinued for all subjects as of 18 Aug 2016. At the time of Amendment 2, Phase 1 was completed, and Phase 2 was initiated at the +1 dose level (PLD 40 mg/m^2, MEDI4736 1500 mg Q4W). Subjects who initiated treatment prior to August 18, 2016 continued the trial at their respective dose levels for PLD and MEDI4736; however, motolimod was discontinued.

This 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 LUD2014-001. The statistical methods and analyses described here are based on those presented in the study protocol (Amendment 4 dated 08SEP2017).

2 STUDY SUMMARY

2.1 STUDY OBJECTIVES

For the Phase 1 study period, the primary objective is to determine the maximum tolerated dose (MTD) and the safety profile of the combination.

For the Phase 2 study period, the primary objective is the evaluation of clinical efficacy as measured by the Progression-free Survival (PFS) rate using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria at 6 months.

For all Phase 1 and 2 cohorts, the secondary objectives are the evaluation of clinical efficacy as measured by overall response rate (ORR), PFS rate at 12 months (and 6 months in Phase 1), overall survival (OS), and biological activity defined as immunological responses.

Safety will be assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Clinical efficacy will be assessed using RECIST v1.1 and irRECIST criteria.

2.2 STUDY DESIGN

This is an open-label, non-randomized, multicenter Phase 1/2 study of motolimod and MEDI4736 in subjects with recurrent, platinum-resistant ovarian cancer, scheduled to receive pegylated liposomal doxorubicin (PLD). The estimated study duration is 39 months (duration of treatment: 12 months, study follow-up: 3 months, post study follow-up: 3 years from initiation of treatment).

Per Amendment 2 (05-OCT-2016), motolimod dosing was discontinued for all subjects as of August 18, 2016. At the time of Amendment 2, Phase 1 was completed, and Phase 2 was initiated at the +1 dose level (PLD 40 mg/m^2, MEDI4736 1500 mg Q4W). Subjects who initiated treatment prior to August 18, 2016 continued the trial at their respective doses levels for PLD and MEDI4736; however, motolimod was discontinued. Prior to Amendment 2, all subjects were treated with PLD intravenously, MEDI4736 intravenously and motolimod subcutaneously during each 28-day cycle. On days with concurrent motolimod and MEDI4736 dosing, motolimod administration was given 30-60 minutes after the end of the MEDI4736 infusion.

Phase 1 dose escalations and de-escalations for the determination of the MTD (or highest tolerable dose tested) were performed based on the available dose levels and the respective rules for a standard 3 + 3 study design, as per Dose Level Table and Schema below:

Dose Level Table

Dose Level	**Pegylated liposomal doxorubicin [mg/m2 IV] day 1**	**MEDI4736 [IV]**	**Motolimod [mg/m^2 SC]**
-1	40	450 mg Q4W **Day 3**	2.0 Days 3, 10 and 17 Cycles 1-3 and day 3 Cycles 4-12
0a (Starting Level)	40	3 mg/kg Q2W **Days 3 and 17** (equivalent to 450 mg Q4W)	2.5 Days 3, 10 and 17 Cycles 1-3 and days 3 and 17 Cycles 4-12
0b (Started with Level 0a)	40	1500 mg Q4W **Day 3**	2.0 Days 3, 10 and 17 Cycles 1-3 and day 3 Cycles 4-12
+1	40	1500 mg Q4W **Day 3**	2.5 Days 3, 10 and 17 Cycles 1-3 and day 3 Cycles 4-12

Q2W = every 2 weeks; Q4W = every 4 weeks
Note for fixed dose of 1500 mg MEDI4736: If a subject's body weight drops to ≤ 30 kg while on the study, the MEDI4736 dose will be 600 mg Q4W as long as the subject's body weight remains ≤ 30 kg.

Phase 2 subjects are treated at the MTD level determined in Phase 1. Subjects are followed on study for 90 days after the last drug administration and off-study every 3 months thereafter for 3 years from initiation of treatment.

Subjects are enrolled in a non-randomized, competitive multicenter, sequential enrollment manner with central subject registration. Subject enrollment and the safety

of the combination regimen are reviewed on an ongoing basis by an internal data safety monitoring panel.

For each cohort in Phase 1, the start of the Cycle 1 Day 3 study drug administration (MEDI4736 + motolimod) for the first and second subject was separated by at least 24 hours. All subjects' safety data is reviewed for DLTs, before proceeding with a cohort expansion or to a dose-escalated/de-escalated cohort.

Per Amendment 1 (09-DEC-2015), the cohort at dose level 0b was added to Phase 1. Depending on the timing of Amendment 1, dose level 0b cohort could be running concurrently with the cohort at dose level 0a, -1, or +1. Thus, subject enrollment will occur as follows:

a) When only 1 cohort is open: sequential enrollment;

b) When 2 parallel cohorts are open: preferential sequential enrollment into the cohort with the higher motolimod dose level or into the cohort with the higher MEDI4736 dose level if both cohorts have the same motolimod dose level.

Subject enrollment is centrally administered.

Enrollment in Phase 2 was initiated after the MTD was established in Phase 1. One patient was enrolled in Phase 2 when motolimod dosing was discontinued for all subjects. The Phase 2 dosing schedule is as follows:

Phase 2 Dosing Schedule	
DAY	**CYCLES 1 – 12**
1	Pegylated liposomal doxorubicin (IV) 40 mg/m^2
3	MEDI4736 (IV) 1500mg

Per Amendment 3 (05-DEC -2016), an optional MEDI4736 treatment extension beyond the initial 12-cycle treatment period (Core Study) was added for subjects who complete the Core Study with Stable Disease or better. The optional treatment extension was permitted for up to 12 additional cycles upon agreement with subject, Sponsor and Investigator, and continued until confirmed disease progression, unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met. Under Amendment 4 (08-SEP-2017), the duration of the optional MEDI4736 treatment extension was changed from 12 cycles to "until confirmed disease progression."

Subjects who receive optional study treatment extension receive the currently recommended fixed dose of 1500 mg MEDI4736 Q4W for subjects > 30 kg. If a subject's body weight drops to ≤ 30 kg, the subject will receive weight-based dosing equivalent to 20 mg/kg Q4W for MEDI4736 as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of MEDI4736 1500 mg.

2.2.1 Number of Subjects

Approximately 6 to 9 sites; and 6 to 53 evaluable subjects were anticipated per the protocol for this study:

Phase 1: 6-18 evaluable subjects to identify the MTD.

Phase 2: 41 evaluable subjects, including the 6 subjects treated in Phase 1 at the MTD.

2.2.2 Randomization and Blinding Procedures

This is an open-label study; therefore, no randomization or blinding procedures are used.

2.2.3 Efficacy Assessments

The assessment of clinical efficacy is the primary objective of Phase 2 and the secondary objective of Phase 1 and is evaluated using RECIST v1.1 and irRECIST criteria.

2.2.3.1 Progression-free Survival Rate

The Phase 2 primary endpoint is the proportion of subjects who survive and do not progress, PFS rate, within the first 6 months of treatment. This endpoint will be based on RECIST v1.1 criteria. The PFS status at 6 months will be based on disease assessments at the scheduled visit at the start of Cycle 7.

The Phase 2 secondary endpoints include PFS rate at 6 months based on irRECIST and PFS rate at 12 months based on RECIST v1.1 and irRECIST.

For Phase 1, the PFS rate at 6 and 12 months based on RECIST v1.1 and irRECIST are secondary endpoints.

2.2.3.2 Progression-free Survival Time

Median PFS time evaluated using RECIST v1.1 and irRECIST criteria is a Phase 1 and Phase 2 secondary endpoint.

PFS time will be defined as the number of days from the date of first dose to the date of earliest disease progression based on radiological or clinical assessment or to the date of death, if disease progression does not occur. Every effort will be made to follow subjects for PFS if they complete or discontinue the study prior to progression.

2.2.3.3 Overall Response Rate

The Phase 1 and Phase 2 secondary endpoints also include ORR based on RECIST v1.1 and irRECIST. ORR is defined as the percentage of subjects meeting criteria of complete response (CR) or partial response (PR) over a period of at least 4 weeks.

2.2.3.4 Overall Disease Control Rate

Overall Disease Control Rate (ODCR) is defined as stable disease (SD), PR, or CR over a period of at least 4 weeks.

2.2.3.5 Overall Survival Time

OS time is a secondary endpoint for Phase 1 and Phase 2 and is defined as the interval of time initiating at the date of study day 1 up to the recorded date of death or last follow-up. 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.

2.2.4 Safety Assessments

Laboratory tests, vital sign measurements, physical exams and subject interviews are performed to detect new abnormalities and deteriorations of any pre-existing conditions. The investigator evaluates any laboratory abnormalities for clinical significance, and clinically significant abnormalities are recorded as adverse events. All clinically significant abnormalities and deteriorations from time of signing of informed consent to the end of study visit should be recorded in the Case Report Form(CRF) as adverse events and graded according to the National Cancer Institute CTCAE version 4.03.

2.2.5 Biological Activity

Samples for exploratory assessment of correlative immunologic research are collected according to the Study Flowchart in Section 3.2 of the protocol. [redacted]

The analyses of these data are being performed by another entity and are not included in the analysis section of this SAP.

Table 1. Schedule of Events

Study Flowchart for Subjects in Dose Level 0a Cohort Only	Screening / Baseline	Treatment																	
		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6		
Cycle week		1		3	1		3	1		3	1		3	1		3	1		3
Visit Day per Cycle	-28 to -1	1	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2
Target Cumulative Visit Day		1	3	17	29	31	45	57	59	73	85	87	101	113	115	129	141	143	157
Phase 1 & 2 STUDY DRUG ADMINISTRATION																			
Pegylated liposomal doxorubicin - PLD (IV)		X			X			X			X			X			X		
MEDI4736 (IV)			X	X		X	X		X	X		X	X		X	X		X	X
Tumor & Disease Assessments																			
Disease Staging (date/stage at 1st diagnosis and at study entry)	X																		
Disease Assessment by RECIST 1.1 and irRECIST (including appropriate imaging)	-14 to -1										X								
Study Procedures & Examinations																			
Eligibility Assessment and Informed Consent (IC)[i]	X																		
Demographics (incl. DoB; sex; race; ethnicity)	X																		
Medical history	X																		
Physical Exam (incl. weight and ECOG Perf Status)	X	X			X			X			X			X			X		
Height	X																		
Vital Signs (T, HR, BP, RR)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[a]	X				X			X			X			X			X		
Echocardiogram or MUGA	X									X									X
Concomitant Medication / Procedure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (starting or worsening after IC)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Specimens for Laboratory Procedures																			
Blood Hematology (complete blood count, differential, platelets)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, PO4, Mg, prot., alb., Tbili., AST, ALT, ALP, LDH)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry cont. (Free T3, Free T4, TSH)[a]	X	X		X	X		X	X		X	X		X	X		X	X		X
Serum pregnancy test[a,f]	-7 to -1							X						X					
CA-125[a]	-14 to -1				X			X			X			X			X		
Urine Pregnancy Test[a,f]		X[a]																	
Specimens for Correlative Assessments																			
PBMC/Plasma Collection & Banking[a,g]	X				X			X											
MDSC (Serametrix)[a,g] (US sites only)	X							X											
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)[e]	X				X	X (at disease progression: optional)													
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[c]	X[g]																		
PAX RNA[a,g]	X				X	X (at disease progression: optional)													

a - pre-dose (when applicable) Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.

b - See Section 6.3.5 for assessment of vital signs before/during/after MEDI4736 infusion

c –An aliquot of the PBMC and/or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed

d - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

e - Biopsy is optional for Phase 1. Refer to Criterion 4 in Section 5.1. Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.

f - Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, #17

g- Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day 1 prior to the PLD dose.

h - See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit.

i - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.

Study Flowchart for Subjects in Dose Level 0a Cohort Only (Cont)	Treatment																		On Study Follow-up			Post Study Follow-Up
	Cycle 7			Cycle 8			Cycle 9			Cycle 10			Cycle 11			Cycle 12			Last Study Drug Administration +14 ±3 days[h]	Last Study Drug Administration +42 ±7 days	Last Study Drug Administration +90 ±7 days End of Study	
Cycle week	1		3	1		3	1		3	1		3	1		3	1		3				
Visit Day per Cycle	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2				
Target Cumulative Visit Day	169	171	185	197	199	213	225	227	241	253	255	269	281	283	297	309	311	325				
Phase 1 & 2 STUDY DRUG ADMINISTRATION																						
Pegylated liposomal doxorubicin - PLD (IV)	X			X			X			X			X			X						
MEDI4736 (IV)		X	X		X	X		X	X		X	X		X	X		X	X				
Tumor & Disease Assessments																						
Disease Staging (date/stage at 1st diagnosis and at study entry)																						
Disease Assessment by RECIST and irRECIST (including appropriate imaging)	X									X									+84 ± 7 days from last disease assessment			
Study Procedures & Examinations																						
Eligibility Assessment and Informed Consent (IC)[i]																						
Demographics (incl. DoB; sex; race; ethnicity)																						
Medical history																						
Physical Exam (incl. weight and ECOG Perf Status)	X			X			X			X			X			X			X	X	X	
Height																						
Vital Signs (T, HR, BP, RR)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[a]	X			X			X			X			X			X			X			
Echocardiogram or MUGA									X										X			
Concomitant Medication / Procedure (name, indication, dose, route, start & end dates)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events (starting or worsening after IC)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Specimens for Laboratory Procedures																						
Blood Hematology (complete blood count, differential, platelets)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, PO4, Mg, prot., alb., Tbili., AST, ALT, ALP, LDH)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Free T3, Free T4, TSH)[a]	X		X	X		X	X		X	X		X	X		X	X		X	X	X	X	
Serum pregnancy test[a,f]	X						X						X						X		X	
CA-125[a]	X			X			X			X			X			X			X			
Urine Pregnancy Test[a,f]																						
Specimens for Correlative Assessments																						
PBMC/Plasma Collection & Banking[a,g]	X																		X		X	
MDSC (Serametrix)[a,g] (US sites only)	X																		X			
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)[e]	X (at disease progression: optional)																					
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[c]																						
PAX RNA[a,g]	X (at disease progression: optional)																					
a - pre-dose (when applicable) Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.																						
b - See Section 6.3.5 for assessment of vital signs before/during/after MEDI4736 infusion																						
c –An aliquot of the PBMC and/or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed																						
d -See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.																						
e - Biopsy is optional for Phase 1. Refer to Criterion 4 in Section 5.1. Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.																						
f - Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, #17																						
g- Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day 1 prior to the PLD dose.																						
h - See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit.																						
i - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart																						

Every 3 months for 3 years from initiation of treatment.
Clinical outcomes data (dates of progression/relapse and survival) will be recorded (See Section 3.1.16).

Study Flowchart for All Subjects Except Dose Level 0a Cohort	Screening / Baseline	Treatment											
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Cycle week		1		1		1		1		1		1	
Visit Day per Cycle	-28 to -1	1	3±1	1±3	3±1	1±3	3±1	1±3	3±1	1±3	3±1	1±3	3±1
Target Cumulative Visit Day		1	3	29	31	57	59	85	87	113	115	141	143
Phase 1 & 2 STUDY DRUG ADMINISTRATION													
Pegylated liposomal doxorubicin - PLD (IV)		X		X		X		X		X		X	
MEDI4736 (IV)			X		X		X		X		X		X
Tumor & Disease Assessments													
Disease Staging (date/stage at 1st diagnosis and at study entry)	X												
Disease Assessment by RECIST 1.1 and irRECIST (including appropriate imaging)	-14 to -1							X					
Study Procedures & Examinations													
Eligibility Assessment and Informed Consent (IC)[i]	X												
Demographics (incl. DoB; sex; race; ethnicity)	X												
Medical history	X												
Physical Exam (incl. weight and ECOG Perf Status)	X	X		X		X		X		X		X	
Height	X												
Vital Signs (T, HR, BP, RR)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[a]	X			X		X		X		X		X	
Echocardiogram or MUGA	X								X				X
Concomitant Medication / Procedure	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (starting or worsening after IC)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Specimens for Laboratory Procedures													
Blood Hematology (complete blood count, differential, platelets)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, PO4, Mg, prot., alb., Tbili., AST, ALT, ALP, LDH)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry cont. (Free T3, Free T4, TSH)[a]	X	X		X		X		X		X		X	
Serum pregnancy test[a,f]	-7 to -1					X				X			
CA-125[a]	-14 to -1			X		X		X		X		X	
Urine Pregnancy Test[a,f]		X[a]											
Specimens for Correlative Assessments													
PBMC/Plasma Collection & Banking[a,g]	X			X		X							
MDSC (Serametrix)[a,g] (US sites only)	X					X							
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)[e]	X			X	X (at disease progression: optional)								
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[c]	X[g]												
PAX RNA[a,g]	X			X	X (at disease progression: optional)								

a - pre-dose (when applicable) Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.

b - See Section 6.3.5 for assessment of vital signs before/during/after MEDI4736 infusion

c –An aliquot of the PBMC and/or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed

d - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

e - Biopsy is optional for Phase 1. Refer to Criterion 4 in Section 5.1. Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.

f - Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, #17

g- Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day 1 prior to the PLD dose.

h - See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit.

i - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart

Study Flowchart for All Subjects Except Dose Level 0a Cohort (Cont)	Treatment												On Study Follow-up			Post Study Follow-Up
	Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		Last Study Drug Administration +28 ±3 days[h]	Last Study Drug Administration +56 ±7 days	Last Study Drug Administration +90 ±7 days End of Study	
Cycle week	1		1		1		1		1		1					
Visit Day per Cycle	1±3	3±1	1 ±3	3 ±1	1 ±3	3 ±1	1 ±3	3 ±1	1 ±3	3 ±1	1 ±3	3 ±1				
Target Cumulative Visit Day	169	171	197	199	225	227	253	255	281	283	309	311				
Phase 1 & 2 STUDY DRUG ADMINISTRATION																
Pegylated liposomal doxorubicin - PLD (IV)	X		X		X		X		X		X					
MEDI4736 (IV)		X		X		X		X		X		X				
Tumor & Disease Assessments																
Disease Staging (date/stage at 1st diagnosis and at study entry)																
Disease Assessment by RECIST and irRECIST (including appropriate imaging)	X						X						+84 ± 7 days from last disease assessment			
Study Procedures & Examinations																
Eligibility Assessment and Informed Consent (IC)[i]																
Demographics (incl. DoB; sex; race; ethnicity)																
Medical history																
Physical Exam (incl. weight and ECOG Perf Status)	X		X		X		X		X		X		X	X	X	
Height																
Vital Signs (T, HR, BP, RR)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[a]	X		X		X		X		X		X		X			
Echocardiogram or MUGA						X							X			
Concomitant Medication / Procedure (name, indication, dose, route, start & end dates)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events (starting or worsening after IC)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Specimens for Laboratory Procedures																
Blood Hematology (complete blood count, differential, platelets)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, PO4, Mg, prot., alb., Tbili., AST, ALT, ALP,LDH)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Free T3, Free T4, TSH)[a]	X		X		X		X		X		X		X	X	X	
Serum pregnancy test[a,f]	X				X				X				X		X	
CA-125[a]	X		X		X		X		X		X		X			
Urine Pregnancy Test[a,f]																
Specimens for Correlative Assessments																
PBMC/Plasma Collection & Banking[a,g]	X												X		X	
MDSC (Serametrix)[a,g] (US sites only)	X												X			
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)[e]	X (at disease progression: optional)															
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[c]																
PAX RNA[a,g]	X (at disease progression: optional)															

Every 3 months for 3 years from initiation of treatment.
Clinical outcomes data (dates of progression/relapse and survival) will be recorded (See Section 3.1.16).

a - pre-dose (when applicable) Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.

b - See Section 6.3.5 for assessment of vital signs before/during/after MEDI4736 infusion

c -An aliquot of the PBMC and/or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed

d - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

e - Biopsy is optional for Phase 1. Refer to Criterion 4 in Section 5.1. Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.

f - Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, # 17

g- Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day 1 prior to the PLD dose.

h - See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit.

i - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart

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 Reporting of Numerical Values

All clinical study data will be presented in subject data listings. All by-visit summarizations will be conducted using data from Cycle 1, Cycle 2, and/or the last cycle, as applicable. All data presentations will be by the planned cohorts in the protocol, separately for Phase 1 and Phase 2.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by cohort for continuous variables.

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

Means and medians will be reported to one decimal place more than the data reported in the EDC. 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 captured in the EDC.

3.1.3 Baseline Value and Change from Baseline

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

3.1.4 Handling of Missing/Incomplete Values

Unless otherwise explicitly specified, missing data will not be imputed.

3.1.5 Handing of Repeated Assessments

If multiple results are available for a test at the same scheduled time point post-baseline then the following rules will be used:

- If multiple pre-dose assessments are available at the same scheduled time point and all results are considered normal, then the first (earliest) result will be used in all summarizations.
- If multiple pre-dose assessments are available at the same scheduled time point and at least one result is considered abnormal, then the worst (most abnormal) result will be used in the summarization.

3.2 Analysis Populations

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 PLD, motolimod (pre Amendment 2), or MEDI4736. All tables, listings, and figures will identify this group of subjects as the Intent-to-Treat Population.

3.2.2 Per-Protocol Population

The Per-Protocol (PP) Population is defined as all subjects enrolled in Phase 2 of the study, including the 6 subjects treated in Phase 1 at the MTD, who received at least 75% of the scheduled doses of MEDI4736 and PLD over the first 2 cycles, as well as respective disease assessments, without major protocol violations.

Phase 2: The Per-Protocol (PP) Population for Phase 2 is defined as all subjects enrolled in Phase 2 of the study who received at least 75% of the scheduled doses of MEDI4736 and PLD over the first 2 cycles, as well as respective disease assessments, without major protocol violations.

3.3 Analysis Variables

3.3.1 Clinical Efficacy

Tumor response will be assessed using RECIST v1.1 and irRECIST criteria. When a radiological assessment is unavailable to determine RECIST (irRECIST), a clinical assessment of progressive disease and/or death may be used in lieu of the RECIST (irRECIST) to determine disease response. This combined clinical efficacy endpoint will be used in the primary efficacy analysis. RECIST and irRECIST criteria are described in detail in the protocol, and an abbreviated description is provided below.

RECIST evaluation of target lesions are as follows:

Response	Criteria for Response
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions taking as reference the baseline sum diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least 20% increase in the sum of the diameters of target lesions taking as reference the baseline sum diameters or new lesion identification

irRECIST evaluation of target and new lesions are as follows:

Complete Response (irCR)	Complete disappearance of all target and new, measurable lesions, with the exceptions of lymph nodes which must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease in TMTB* ≥ 30% relative to baseline.
Stable Disease (irSD)	Not meeting criteria for irCR or irPR, in absence of irPD.
Progressive Disease (irPD)	Increase in TMTB ≥ 20% relative to nadir.

*TMTB = SumD target lesions + SumD new, measurable lesions.

For both RECIST and irRECIST, if CA125 levels are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Efficacy variables include:

- Progression-free Survival
    - Proportion of subjects surviving without progression at 6 months (based on RECIST v1.1 and/or clinical progression/death) – Phase 2 primary endpoint
    - Proportion of subjects surviving without progression at 6 months (based on irRECIST and/or clinical progression/death) – Phase 2 secondary endpoint
    - Proportion of subjects surviving without progression at 12 months (based on RECIST v1.1 and irRECIST and/or clinical progression/death) – Phase 2 secondary endpoints
    - Proportion of subjects surviving without progression at 6 and 12 months (based on RECIST v1.1 and irRECIST and/or clinical progression/death) – Phase 1 secondary endpoints
    - Progression-free survival time (based on RECIST v1.1 and irRECIST and/or clinical progression/death) – Phase 1 and 2 secondary endpoints

- Tumor Response
    - Overall Response Rate (ORR) based on RECIST v1.1 and irRECIST and/or clinical progression/death – Phase 1 and 2 secondary endpoints
    - Overall Disease Control Rate – stable disease (SD), PR, or CR over a period of at least 4 weeks based on RECIST v1.1 and irRECIST- Phase 1 and 2 secondary endpoints
- Overall Survival
    - Median overall survival time – Phase 1 and 2 secondary endpoint

3.3.2 Safety Variables

Safety variables include:

- Incidence of treatment emergent adverse events (TEAEs), defined as an adverse event (AE) that is first identified, or is identified to worsen in intensity, at a time point occurring after the first dose of study drug
    - All TEAEs by System Organ Class (SOC) and Preferred Term (PT)
    - All TEAEs by PT
    - TEAEs by maximum severity (according to CTCAE version 4.03)
    - Treatment related TEAEs (TRAE) defined as events with a relationship to any study drug of 'Definitely Related', 'Probably Related' or Possibly Related'
    - Treatment related TEAEs by maximum severity (according to CTCAE version 4.03)
    - TEAEs leading to study drug withdrawal
    - Serious TEAEs
- Change in clinical laboratory parameters (hematology, chemistry, amylase, lipase, thyroid) from baseline to each selected post-treatment assessment time point and shifts in clinical laboratory parameters from baseline to each selected post-treatment assessment time point
- Change in vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) from pre-dose to end of infusion at selected post-treatment assessment time points
- Change in ECOG performance status from baseline to last assessment
- Shifts in ECG from baseline to each selected post-treatment assessment time point

- Shifts in ECHO or MUGA from baseline to each selected post-treatment assessment time point

3.3.3 Immunological Response

The following immunological response variables are being analyzed by another entity and are not included in the analysis sections below:

[redacted]

3.4 Subjects Disposition and Evaluability

3.4.1 Subject Disposition

Subject disposition will be presented by cohort and overall. The number of subjects enrolled and in the ITT and PP populations will be presented.

The following will be summarized:

- number and percentage of ITT subjects experiencing a DLT
- number and percentage of ITT subjects discontinuing study treatment and the reasons for treatment discontinuation
- number and percentage of ITT subjects completing and not completing the study (through 90 day on Study Follow-up period), and the reasons for study discontinuation
- number and percentage of ITT subjects entering and discontinuing from the Follow-up Extension, and the reasons for discontinuation

Descriptive statistics will also be presented for duration of time in study for subjects (start of therapy to last visit of follow-up).

3.4.2 Protocol Deviations

Protocol violations and deviations are recorded in a written log. Any major protocol deviations will be described in the study report.

3.5 Demographics and Baseline Characteristics

3.5.1 Demographics

Subject demographics, height and weight will be summarized for the ITT and PP populations.

Descriptive statistics will be provided for age (years), height (cm), and weight (kg). Frequencies and percentages will be tabulated for sex, race, ethnicity, disease staging at initial diagnosis and study entry, and for prior anti-cancer treatment use and the corresponding indications.

3.5.2 Medical History

The number and percentage of subjects having a non-oncological medical condition in each body system will be summarized for the ITT Population. Non-oncological medical history will be presented in a subject listing.

3.5.3 Oncological Treatment History

. Prior oncological treatment, radiation and surgical history will be presented in subject listings.

3.6 Prior and Concomitant Medications/Procedures

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary (Version Dec 2014).

A concomitant medication is defined as any drug or substance administered between the time of the first dose of study treatment and the time of the last study visit. This includes medications that were started prior to screening, if their use continued during or after dosing. In order to define whether a medication with missing start or stop dates is a concomitant medication, refer to the following additional criteria.

- 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.

Concomitant medication use will be classified by Anatomical Therapeutic Class (ATC) level 4 and PT for the ITT population. For the presentation of concomitant medications, the ATC level 4 terms will be sorted alphabetically, and within ATC level 4 term, the PT will be used and presented by decreasing total frequency overall.

Frequencies and percentages of subjects using each concomitant medication will be presented for the ITT population. Prior and concomitant medications and concomitant procedures/surgeries will be presented in subject listings.

3.7 Treatment Exposure

For each subject, treatment duration and the total number of cycles treated will be calculated based on the expected treatments for that subject in accordance with their assigned cohort. Treatment duration (weeks) will be calculated for each subject as: ([date of last dose of any study drug received – date of first dose of any study drug received +1]/7).

Descriptive statistics for treatment duration and the total number of treatment cycles will be displayed. The number of doses and cumulative dose received will be summarized for PLD, MEDI4736, and Motolimod. Study drug administration will be presented in a subject listing.

3.8 Efficacy Analysis

3.8.1 Progression-free Survival

The primary endpoint in Phase 2 of this study is the PFS rate at 6 months defined as the visit at the start of Cycle 7, where progression is assessed for subjects based on a combination of RECIST v1.1 and/or the clinician's assessment of clinical progression or death. The primary efficacy analysis will be based on the Per Protocol population. A sensitivity analysis will be conducted on the ITT population. A secondary efficacy analysis will be conducted on the Phase 2 Per Protocol population.

The primary efficacy analysis entails testing the null hypothesis that PFS at 6 months is less than or equal to 25% against the alternative hypothesis that PFS at 6 months is higher for those treated with PLD and MEDI4736 combination. This hypothesis will be tested at α=0.05 using the 90% two-sided confidence interval for the PFS rate at 6 months based on Kaplan-Meier product limit estimates. The null hypothesis will be rejected in favor of the alternative if the lower bound of that confidence interval is greater than 25%. The null hypothesis will also be tested using a one-sided binomial test as a sensitivity analysis. In this analysis, if a subject has no tumor response assessment, or discontinued treatment or withdrew from the study for other reasons, he or she will be considered as "progressed." The null hypothesis will be rejected in favor of the alternative if the lower bound of a two-sided 90% binominal confidence interval is greater than 25%.

Table displays will include PFS rate at 6 months and the corresponding 90% confidence interval along with the corresponding number of subjects at risk. In addition, PFS will be presented graphically.

Secondary efficacy analyses will use the secondary efficacy endpoints listed in section 3.3.1 of the SAP and will be based on the ITT population. PFS rate and the corresponding 95% confidence interval will be calculated based on Kaplan-Meier product limit estimates and will be displayed by cohort and phase.

Descriptive analyses of PFS will include the following:

- Number and percentage of subjects that died or had a confirmed progression,
- Number and percentage of subjects that survived without a confirmed progression,
- Number and percentage of subjects lost to follow up (unknown survival and/or progression status), and
- Number of subjects missing the tumor response assessment

PFS time will be summarized for each cohort and phase and will include the 25th percentile, median, 75th percentile, corresponding 95% CIs, minimum and maximum, where PFS time will be calculated using the Kaplan-Meier method. In addition, PFS will be presented graphically.

PFS time is defined as time from the start date of the treatment (Day 1) to the first occurrence of confirmed progression (clinical or radiological), or the date of death due to any cause, whichever occurs first. Subjects without documentation of progression at the time of the analysis will be censored at the date of the last tumor response assessment, date of start of alternate therapy, or last contact if in post study follow-up, whichever comes first. Subjects with no tumor response assessment will be censored at the start date of the treatment.

3.8.2 Tumor Response

Tumor response will be summarized and analyzed descriptively for the ITT population.

The number and percentage of subjects meeting criteria of CR, PR, SD, and PD will be displayed. The number and percentage of subjects meeting criteria of CR or PR over a period of at least 4 weeks (Overall Response Rate – ORR) based on RECIST v1.1 and irRECIST, as well as the number and percentage of subjects meeting criteria of SD, PR, or CR over a period of at least 4 weeks (Overall Disease Control Rate – ODCR) will be displayed along with the corresponding 95% binomial CIs. In calculating ORR and ODCR, subjects who drop out prior to meeting the responder criteria will be considered as non-responders. Descriptive statistics 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. Tumor response and tumor marker CA-125 will be presented in subject listings.

3.8.3 Overall Survival

Overall survival (OS) time will be based on data collected during study and Post Study Follow-up. OS time is defined as the time from the start date of the treatment (Day 1) to the date of death due to any cause and will be analyzed descriptively.

The number and percentage of subjects who died, who were lost to follow up, and who survived will be summarized. Subjects who withdrew from the study or were lost to follow-up (survival status unknown) will be censored at the date of last contact/last data point collected in the CRF.

OS Rate and the corresponding 95% confidence intervals at 6 months and 12 months will be calculated based on Kaplan-Meier product limit estimates and will be displayed along with the corresponding number of subjects at risk at each time point. OS time will be summarized descriptively. The 25th percentile, median, 75th percentile, corresponding 95% CIs as well as the minimum and maximum survival time will be calculated using the Kaplan-Meier method. In addition, OS estimates will be presented graphically.

3.9 Safety Analysis

All safety analyses will be performed using the ITT population. For clinical laboratory, data collected from all core study cycles and/or on-study follow-up assessments will be analyzed for each subject. For vital signs, ECOG performance status, and ECG, only data collected from the first two cycles and/or on-study follow-up assessments will be analyzed for each subject. All subject data including those from the additional cycles will be presented in subject listings.

3.9.1 Adverse Events

All adverse events 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).

The following imputation rules will be used for missing or incomplete AE start dates:

- 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.

3.9.1.1 Overall Summary of Treatment Emergent Adverse Events

An overall summary of TEAEs will be presented by cohort and for all subjects combined. The number and percentage of subjects who experienced at least one AE, at least one TEAE, at least one TRAEs, at least one TEAE of Grade 3 or higher, at least one TRAE of Grade 3 or higher, at least one serious TEAE, at least one DLT, at least one serious TRAE, at least one TEAE leading to treatment discontinuation, at least one TRAE leading to treatment discontinuation, and number of subjects with an adverse event resulting in death will be displayed.

3.9.1.2 Treatment Emergent Adverse Event Incidences

The incidence of TEAEs will be presented by cohort and for all cohorts combined. The number and percentage of subjects who experienced at least one TEAE as well as the number and percentage of subjects who experienced at least one TEAE within each specific SOC and PT will be presented. For this analysis, 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.

A summary table of TEAEs by PT will also be presented by cohort and for all cohorts combined.

For the presentation of AE incidences, the SOCs will be sorted alphabetically, and within SOC, the preferred term (PT) will be presented by decreasing total frequency.

Adverse events leading to study withdrawal, leading to study drug interruption or discontinuation, treatment emergent adverse events, serious adverse events, dose-limiting toxicities, and deaths will be displayed in subject listings.

3.9.1.3 Adverse Events by Maximum CTCAE Grade

TEAEs will be presented by maximum CTCAE grade for each PT by cohort and for all subjects combined. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject under the maximum grade at which it was experienced.

3.9.1.4 Treatment Related Adverse Events

Adverse events with a relationship to study drug of "possibly," "probably" or "definitely" related will be classified as treatment related.

The number and percentage of subjects who experienced at least one treatment related AE within each specific SOC and PT will be presented overall and by cohort. For the presentation of AE incidences, the SOCs will be sorted alphabetically, and within SOC, the preferred term (PT) will be presented by decreasing total frequency.

The incidences of adverse events related to MEDI4736, motolimod, and PLD will also be summarized by SOC and PT.

Incidence of treatment related AEs will be presented by maximum CTCAE grade for each PT by cohort. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject under the maximum grade at which it was experienced.

The incidences of adverse events related to MEDI4736, motolimod, and PLD will also be presented by maximum CTCAE grade for each PT overall and by cohort.

3.9.1.5 TEAEs Leading to Study Drug Withdrawal

TEAEs leading to study drug withdrawal of MEDI4736, motolimod, or PLD will be presented by SOC and PT and will also be presented in a subject listing.

3.9.1.6 DLTs

DLTs will be presented in subject listings.

3.9.1.7 Serious Adverse Events

The incidences of serious adverse events will be summarized by SOC and PT overall and by cohort. SAEs will be presented in a subject listing.

3.9.2 Clinical Laboratory Evaluation

For each continuous laboratory (hematology and chemistry) parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented by cohort and overall for the shifts in these categories from baseline to selected post-treatment assessment time points (i.e., low to normal, low to high, high to low, etc.). Percentages for the shift tables will be calculated based on the number of subjects who had results for both baseline and the corresponding post-treatment assessment time point. Additionally, for continuous hematology and chemistry parameters, descriptive statistics will be presented for the changes from baseline to each selected post-treatment assessment time point.

Abnormal laboratory values with their clinical significance status will be presented in a subject listing.

3.9.3 Vital Signs

For vital signs, descriptive statistics will be presented for changes from pre-dose to end of infusion on MEDI4736 dosing days in the first two cycles and for On Study Follow-up assessments. End of infusion time points and change from pre-dose to end of infusion for subjects who experienced an interruption in the study drug administration (administration was stopped and subsequently restarted) will not be included.

3.9.4 ECOG Performance Status

ECOG Performance Status will be summarized by cohort by presenting the number and percentage of subjects with ECOG score 0, 1, 2, 3, and 4 at baseline and ECOG score of 0, 1, 2, 3, 4, and 5 at the last on-treatment assessment time point (including optional treatment extension time points) and last on-study follow-up time point for which ECOG Performance Status was assessed. ECOG data will be provided in a subject listing.

3.9.5 12-Lead ECG

Shift of normality status (normal, abnormal with no clinical significance, abnormal with clinical significance) from baseline to each selected post-treatment assessment time point will be presented for the ECG data. Based on the number of subjects who had non-missing results for both baseline and corresponding post-treatment assessment time point, percentages for the shift tables will be calculated. ECG results will be provided in a subject listing.

3.9.6 ECHO or MUGA

For the ECHO or MUGA data, shift of normality status (normal, abnormal with no clinical significance, abnormal with clinical significance) from baseline to each selected post-treatment assessment time point will be presented. Percentages for the

shift tables will be calculated based on the number of subjects who had non-missing results for both baseline and corresponding post-treatment assessment time point. ECHO and MUGA data will be provided in a subject listing.

3.9.7 Physical Examination

Physical examination assessments, if performed, will be shown in a subject listing.

4 LIST OF TABLES

5 LIST OF LISTINGS

6 LIST OF FIGURES