STATISTICAL ANALYSIS PLAN

A phase I open-label multicentre dose-escalation study of subcutaneous ALM201 in patients with advanced ovarian cancer and other solid tumours: Part 1 – Dose Escalation

Study Protocol: ALM201/0001

Study Drug(s): ALM201

EudraCT No: 2014-001175-31

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Contents

Abbreviations

AE	adverse event
AUC	area under the plasma concentration versus time curve
BP	blood pressure
CA	Competent Authority/ies
CA-125	cancer antigen-125
CEA	Carcinoembryonic antigen
C_{max}	maximum plasma concentration
C_{min}	minimum observed concentration
CR	complete response
CRC	Cohort Review Committee
CRF	case report form
CT	computed tomography
CTC	circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
LVEF	Left Ventrical Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
PBMC	peripheral blood mononuclear cells
PharmD	pharmacodynamic(s)
PD	progressive disease
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PSA	prostate-specific antigen
PT	Preferred Term
QTcF	QT interval corrected for Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	System Organ Class
t_{max}	time to reach maximum concentration
UK	United Kingdom

1 Introduction

This document presents the statistical analysis plan (SAP) for ALMAC, Protocol No. ALM201/0001: A phase I open-label multicentre dose-escalation study of subcutaneous ALM201 in patients with advanced ovarian cancer and other solid tumours. This analysis plan is based on the final protocol dated 24Sep2014. The study was to be a two-part study, but the sponsor decided to halt the study at the end of part 1. The SAP provides the description of the analysis for the final analyses of Part 1. The Pharmacokinetic Analysis will be conducted separately and presented in a separate document.

2 Study Objectives

2.1 Primary Objectives

The primary objective of this study is/are:

- To characterise the safety and tolerability of ALM201

2.2 Secondary Objectives

- To establish the pharmacokinetic profile of ALM201 (presented in a separate document)
- To assess anti-tumour activity

2.3 Exploratory Objectives

- To assess relevant tumour biomarkers and the pharmacodynamics activity of ALM201.

2.4 Primary end-points

The primary end-points of this study are:

- Ongoing evaluation of Adverse Events (AEs) during treatment and follow up; evaluation of dose limiting toxicity (DLT) during Cycle 1
- Safety, pharmacokinetic (PK), pharmacodynamic (PharmD) and tumour response assessments

2.5 Secondary end-points

The secondary end-points of this study are:

- Assessment of pharmacokinetic variables (including C_{max}, C_{min}, T_{max},AUC) (presented in a separate document)
- Tumour response assessment by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1(Eisenhauer et al, 2009i) and/or other relevant response assessments for tumour types enrolled

2.6 Exploratory end-points

The exploratory end-points of this study are:

Assessment of relevant tumour biomarkers and markers of ALM201 activity in:

- archival and/or fresh tumour biopsy material e.g. CD44, FKBPL, CD31, pFAK, pHer2, ITGA5, CA-125, ER, PR, angiogenesis signature and other relevant or exploratory biomarkers as appropriate for tumour type
- blood e.g. RASSF1 methylation, and other relevant or exploratory appropriate for tumour type

3 Study Design

3.1 Discussion of Study Design

This is a Phase 1, open-label, dose escalation study of the safety, tolerability, and pharmacokinetics (PK) of ALM201. The study will commence by enrolling patients with advanced solid tumours in whom treatment with an anti-angiogenic agent is appropriate. Eligible participants will be enrolled in sequential cohorts treated with ALM201, given as a sub-cutaneous (SC) injection while being monitored for safety and DLTs.

Dose levels will not be weight-adjusted and the starting dose for the study will be 10 mg ALM201 given on Days 1-5, 8-12 and 15-19 every 21 days i.e. weekday dosing. Dose increments will not exceed 100% and will be guided by safety data observed during Cycle 1, as well as on-going assessment of safety beyond Cycle 1 in earlier cohorts, plus PK and PharmD data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 1 of treatment (See Section 4.2.1 of the protocol).

The highest dose where ≤ 1 DLT is seen in 3 or 6 patients will be termed the maximum tolerated dose (MTD). Note that intermediate dose levels may be explored below the dose level where ≥ 2 DLTs were seen, in order to identify the maximum dose which may be adequately tolerated. The Cohort Review Committee (CRC) may also specify a recruitment stagger to be followed during cohort expansion for DLT evaluation depending on the nature of the DLT and the considered risk to patients.

In the case where an MTD is not established, the maximum feasible single dose which may be administered will be dictated by the formulation of ALM201 and the maximum volume for SC administration i.e. 3 x 1 mL injections, which will administer a dose of 300 mg ALM201 (See Section 6 of the protocol). Should this dose be reached without the need to de-escalate due to DLT, it will be termed the maximum feasible dose (MFD).

Based on the review of PharmD data in conjunction with on-going safety and PK data, the CRC may also identify a biologically active dose (BAD) for further exploration in Part 2 of the study.

3.2 Study Treatment

The study will commence with a dosing schedule of ALM201 monotherapy given SC on Days 1-5, 8-12 and 15-19 in a 3 week cycle. ALM201 is formulated as an aqueous solution containing 80mM sodium carbonate, 20mM Tris and 25mM sodium chloride, pH 6.5.

Patients will have scheduled site visits on every dosing day of the first cycle, then on Days 1, 8 and 15 of Cycles 2-4. From Cycle 5 onwards, they are only required to visit the clinic on Day 1 of each cycle. ALM201 administration can be given at home on all other days.

Safety assessments will include physical examination, vital signs, biochemistry and haematology laboratory screens, plus immunogenicity testing (see Schedule of Study Assessments). Adverse events will also be noted at every clinical visit and recorded at least every week.

Tumour assessment by imaging (computed tomography (CT) scan or magnetic resonance imaging (MRI) scan as appropriate for tumour type) will be assessed in all patients at Screening and after every 2 cycles of treatment (i.e. every 6 weeks) during Cycles 1–8 (first 24 weeks), and then after every 4 cycles of treatment (i.e. every 12 weeks) from Cycle 9 onwards. Scans may be performed at other times as clinically indicated.

Tumour assessment by informative tumour markers where relevant for tumour type e.g. GCIG criteria for CA125 (Rustin, et al. 2011ii), prostate-specific antigen (PSA), CEA or CA19-9, will be assessed in all patients at Screening and after every 2 cycles of treatment during treatment (i.e. every 6 weeks). Tumour markers may be performed at other times as clinically indicated.

A PK profile for ALM201 will be taken on Days 1, 3 and 18 of Cycle 1 and on Day 18 of Cycles 2, 4, 6 and 8. Pre-dose samples will also be taken on Cycles 2-8 on Day 1.

3.3 Study Schedule

- **Schedule of Assessments for Starting Dose Administration Schedule: Day 1-5, 8-12 and 15-19 of a 21-day dosing schedule**

	Screening	Cycle 1 (21 d cycle)							Cycle 2 – 4 (21 d cycle)						Cycle 5 – 8 (21 d cycle)							Final Study Visit[11]	Long-term Follow Up
		Day							Day						Day								
	-28 to 0	1	2	3-5	8	9-12	15	16-19	22/1[10]	2-5	8	9-12	15	16-19	22/1[10]	2-5	8	9-12	15	16-19	22/1[10]		
Informed consent	X																						
Demographics	X																						
Medical history	X																						
Inclusion/exclusion	X																						
ECOG PS	X								X						X						X	X	
Physical examination[1]	X	X			X		X		X		X		X		X		X		X		X	X	
Vital signs[2]	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	
ECG (resting 12-lead)[3]	X	X							X						X						X		
Clinical chemistry*	X	X			X		X		X		X		X		X		X		X		X	X	
Echocardiogram	X																						
Haematology	X	X			X		X		X		X		X		X		X		X		X	X	
Coagulation	X	X			X		X		X		X		X		X		X		X		X		
Urinalysis*	X	X							X						X						X		
Tumour assessment (radiological)[4]	X								X[4]						X[4]						X[4]	X[4]	
Tumour assessment (serum marker)[4]	X	X							X						X						X[4]	X[4]	
Immunogenicity assessment		X							X						X						X	X	
Biomarker/PharmD assessment (biopsy)[5]	X	X - up to 2 post-treatment samples																					
Biomarker/PharmD assessment (blood sample)[6]	X	X - up to 12 post-treatment samples																					
Biomarker/PharmD assessment (ascites)[7]	(X)	(X - up to 5 post-treatment samples)																					
Biomarker (germ-line DNA) testing[8]	(X)																						
Adverse events		X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	
ALM201 administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pharmacokinetics[9]		X	X	X				X	X					X	X					X	(X)		
Long-term follow up[12]																							X

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to ALM201 administration, unless specified otherwise.
- Additional assessments may be conducted as clinically indicated.
- (X) denotes an assessment not applicable to all patients.
- A tolerance of +/-1 day will be permitted for all study visits and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

* ***female patients, if fertile, will require a serum pregnancy test at Screening and urine pregnancy on Day 1 of each cycle***

Assessment Specific

1. Patient's height will be recorded at Screening. A full physical examination is required at Screening and prior to Day 1 of each cycle; Symptom-directed physical examination is acceptable at other time-points. Weight will be recorded at Screening and on Day 1 of each cycle.

2. On each hospital administration day, vital signs (heart rate, BP, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after the ALM201 injection. Patient status will be monitored during ALM201 administration and repeat vital signs will be taken if needed.

3. On Cycle 1, Day 1 a resting 12-lead ECG will be conducted pre-dose and 30 mins (+/- 15 mins) after ALM201 injection. On Day 1 of all other cycles, a resting 12-lead ECG will be conducted pre-dose only.

4. CT or MRI performed at Screening and up to 7 days prior to start of Cycle 3, 5, 7 and at the end of Cycle 8. Note that where there is a rationale for assessment of bone lesions, these assessments will be performed as part of the CT or MRI assessment and will not require additional radiological bone scan assessment.

   Other informative markers e.g. CA-125, PSA, photographs of melanoma skin lesions, may be taken as appropriate on Day 1 of each cycle.

   Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per appropriate response assessment guidelines. Any requirement for confirmatory scans will typically be performed at the next protocolled assessment time point. Other assessments e.g. whole body MRI or PET, are not protocol mandated, but may be performed as clinically indicated and at request of Investigator.

5. Patients with available archived biopsy samples will consent to provide these for biomarker/PharmD evaluation. The study will encourage taking fresh biopsies for biomarker/PharmD evaluation at Screening and post-treatment upon tumour response and/or at the point of disease progression. Although optional, every effort should be made to collect fresh pre and post-dose biopsy samples from patients – particularly in Part 2 - and imaging techniques may be used to facilitate this process.

6. Assessment of biomarker/PharmD activity from blood samples taken to obtain serum, plasma, PBMC or CTCs, may be conducted in all patients between Screening, Cycle 6 and Final Study Visit, with no more than 2 samples taken on any study day, 4 in any treatment cycle, and 13 in total during 6 cycles (including Screening and Final Study Visit). Time-points may vary depending on the assay and method of analysis.

7. Assessment of biomarker/PharmD activity in ascites may be conducted in relevant patients who are undergoing draining of ascites as part of their standard of care. This procedure would normally be performed under ultrasound marking. It is estimated that the study may obtain up to 6 samples over 8 cycles (including Screening and Final Study Visit). Actual time-points may vary within each cycle.

8. Consenting patients will have a 10 mL blood sample taken for preparation of a germ-line DNA sample at Screening (recommended time-point only).

9. Patients will have a 12-hour urine collection on Cycle 1, Day 1 for urine PK analysis.

   Patients will have PK blood sampling conducted at Cycle 1 at the following sample times. Three PK profiles may be taken: each will not exceed up to 12 samples taken out to 24 hours post ALM201 injection. The CRC may advise on adjusted time-points. The maximum number of PK samples to be collected during any Cycle 1 dose schedule will not exceed 40. The actual time for each blood draw must be accurately recorded. Initial sampling time points are:

   Cycle 1, Day 1:
   All doses (except 300mg): Predose, then 15 mins (+/- 5 mins), 45 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 3 hr (+/- 10 mins), 4 hr (+/- 10 mins), 5 hr (+/- 10 mins) , 6 hr (+/- 10 mins), 22 hr (+/- 1hr).

   Doses of 300 mg: Predose, then 15 mins (+/- 5 mins), 45 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 3 hr (+/- 10 mins), 4 hr (+/- 10 mins), 5 hr (+/- 10 mins) , 6 hr (+/- 10 mins), 7 hr (+/- 10 mins), 8 hr (+/- 10 mins), 22 hr (+/- 1hr).

   Cycle 1, Day 3 & 18:
   All doses (except 300mg): Predose, then 30mins (+/- 5 mins), 60 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 3.5 hr (+/- 10 mins), 5 hr (+/- 10 mins).

   Doses of 300 mg: Predose, then 30 mins (+/- 5 mins), 60 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 4.5 hr (+/- 10 mins), 7 hr (+/- 1 hr).

   Cycles 2, 4, 6 & 8, Day 18:
   All doses (except 300mg): Predose, then 30mins (+/- 5 mins), 60 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 3.5 hr (+/- 10 mins), 5 hr (+/- 10 mins).

   Doses of 300 mg: Predose, then 30 mins (+/- 5 mins), 60 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 4.5 hr (+/- 10 mins), 7 hr (+/- 1 hr).

   A single pre-dose sample will also be taken on Cycles 2-8 on Day 1.

10. Day 22 of Cycle 1, 2, 3, 4, 5, 6 and 7 is Day 1 of Cycle 2, 3, 4, 5, 6, 7 and 8.

11. The Final Study Visit should be performed 30 +/-3 days after the last dose of ALM201 to enable a final safety assessment.

12. Those patients who do not have disease progression at the Final Study Visit will be contacted every 8 weeks for up to 2 years (approximately) to check their status and commencement of their next anticancer treatment.

- **Schedule of Study Assessments for Alternative Dose Schedules**

	Screening	Cycle 1				Cycle 2 – 4			Cycle 5 – 8				Final Study	Long-term
		Day				Day			Day					
	-28 to 0	1	2	Cthe	Week	22/1	Cth	Wee	22/	Cth	Wee	22/		
Informed consent	X													
Demographics	X													
Medical history	X													
Inclusion/exclusion	X													
ECOG PS	X					X			X			X	X	
Physical examination[1]	X	X			X	X		X	X		X	X	X	
Vital signs[2]	X	X			X	X		X	X		X	X	X	
ECG (resting 12-lead)[3]	X	X				X			X			X		
Echocardiogram	X													
Clinical chemistry*	X	X			X	X		X	X		X	X	X	
Haematology	X	X			X	X		X	X		X	X	X	
Coagulation	X	X			X	X		X	X		X	X		
Urinalysis*	X	X				X			X			X		
Tumour assessment (radiological)[4]	X					X[4]			X[4]			X[4]	X[4]	
Tumour assessment (serum marker)[4]	X	X				X			X			X[4]	X[4]	
Immunogenicity assessment		X				X			X			X		
Biomarker/PharmD assessment (biopsy)[5]	X	X – up to 2 post-treatment samples												
Biomarker/PharmD assessment (blood sample)[6]	X	X - up to 12 post-treatment samples												
Biomarker/PharmD assessment (ascites)[7]	(X)	(X – up to 5 post-treatment samples)												
Biomarker (germ-line DNA) testing[8]	(X)													
Adverse events		X	X	X	X	X		X	X		X	X	X	
Concomitant medication	X	X	X	X	X	X		X	X		X	X	X	
ALM201 administration		X (D1 + additional doses following dosing Schedule)				X (as per dosing schedule)								
Pharmacokinetics[9]		X	X	X		X	X		X	X		(X)		
Long-term follow up[12]														X

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to ALM201 administration, unless specified otherwise.
- Additional assessments may be conducted as clinically indicated.
- (X) denotes an assessment not applicable to all patients.
- A tolerance of +/-1 day will be permitted for all study visits and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

* ***female patients, if fertile, will require a serum pregnancy test at Screening and urine pregnancy on Day 1 of each cycle***

Assessment Specific

1. Patient's height will be recorded at Screening. A full physical examination is required at Screening and prior to Day 1 of each cycle; Symptom-directed physical examination is acceptable at other time-points. Weight will be recorded at Screening and on Day 1 of each cycle.

2. On each hospital administration day, vital signs (heart rate, BP, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after the ALM201 injection. Patient status will be monitored during ALM201 administration and repeat vital signs will be taken if needed.

3. On Cycle 1, Day 1 a resting 12-lead ECG will be conducted pre-dose and 30 mins (+/- 15 mins) after ALM201 injection. On Day 1 of all other cycles, a resting 12-lead ECG will be conducted pre-dose only.

4. CT or MRI performed at Screening and up to 7 days prior to start of Cycle 3, 5, 7 and at the end of Cycle 8. Note that where there is a rationale for assessment of bone lesions, these assessments will be performed as part of the CT or MRI assessment and will not require additional radiological bone scan assessment.

   Other informative markers e.g. CA-125, PSA, photographs of melanoma skin lesions, may be taken as appropriate on Day 1 of each cycle.

   Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per appropriate response assessment guidelines. Any requirement for confirmatory scans will typically be performed at the next protocolled assessment time point. Other assessments e.g. whole body MRI or PET, are not protocol mandated, but may be performed as clinically indicated and at request of Investigator.

5. Patients with available archived biopsy samples will consent to provide these for biomarker/PharmD evaluation. The study will encourage taking fresh biopsies for biomarker/PharmD evaluation at Screening and post-treatment upon tumour response and/or at the point of disease progression. Although optional, every effort should be made to collect fresh pre and post-dose biopsy samples from patients – particularly in Part 2 - and imaging techniques may be used to facilitate this process.

6. Assessment of biomarker/PharmD activity from blood samples taken to obtain serum, plasma, PBMC or CTCs, may be conducted in all patients between Screening, Cycle 6 and Final Study Visit, with no more than 2 samples taken on any study day, 4 in any treatment cycle, and 13 in total during 6 cycles (including Screening and Final Study Visit). Time-points may vary depending on the assay and method of analysis.

7. Assessment of biomarker/PharmD activity in ascites may be conducted in relevant patients who are undergoing draining of ascites as part of their standard of care. This procedure would normally be performed under ultrasound marking. It is estimated that the study may obtain up to 6 samples over 8 cycles (including Screening and Final Study Visit). Actual time-points may vary within each cycle.

8. Consenting patients will have a 10 mL blood sample taken for preparation of a germ-line DNA sample at Screening (recommended time-point only).

9. Patients will have a 12-hour urine collection on Cycle 1, Day 1 for urine PK analysis.

   Patients will have PK sampling conducted at Cycle 1 at the following sample times. Three PK profiles may be taken: each will not exceed up to 12 samples taken out to 24 hours post ALM201 injection. The CRC may advise on adjusted time-points. The maximum number of PK samples to be collected during any Cycle 1 dose schedule will not exceed 40. The actual time for each blood draw must be accurately recorded. Initial sampling time points are:

   Cycle 1, Day 1:
   All doses (except 300mg): Predose, then 15 mins (+/- 5 mins), 45 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 3 hr (+/- 10 mins), 4 hr (+/- 10 mins) , 5 hr (+/- 10 mins) , 6 hr (+/- 10 mins), 22 hr (+/- 1hr).

   Doses of 300 mg: Predose, then 15 mins (+/- 5 mins), 45 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 3 hr (+/- 10 mins), 4 hr (+/- 10 mins), 5 hr (+/- 10 mins), 6 hr (+/- 10 mins), 7 hr (+/- 10 mins), 8 hr (+/- 10 mins), 22 hr (+/- 1hr).

   Cycle 1, Day 3 & 18:
   All doses (except 300mg): Predose, then 30mins (+/- 5 mins), 60 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 3.5 hr (+/- 10 mins), 5 hr (+/- 10 mins).

   Doses of 300 mg: Predose, then 30 mins (+/- 5 mins), 60 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 4.5 hr (+/- 10 mins), 7 hr (+/- 1 hr).

   Cycles 2, 4, 6 & 8, Day 18:
   All doses (except 300mg): Predose, then 30mins (+/- 5 mins), 60 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 3.5 hr (+/- 10 mins), 5 hr (+/- 10 mins).

   Doses of 300 mg: Predose, then 30 mins (+/- 5 mins), 60 mins (+/- 5 mins), 1.5 hr (+/- 10 mins), 2 hr (+/- 10 mins), 4.5 hr (+/- 10 mins), 7 hr (+/- 1 hr).

   A single pre-dose sample will also be taken on Cycles 2-8 on Day 1.

10. Day 22 of Cycle 1, 2, 3, 4, 5, 6 and 7 is Day 1 of Cycle 2, 3, 4, 5, 6, 7 and 8.

11. The Final Study Visit should be performed 30 +/-3 days after the last dose of ALM201 to enable a final safety assessment.

12. Those patients who do not have disease progression at the Final Study Visit will be contacted every 8 weeks for up to 2 years (approximately) to check their status and commencement of their next anticancer treatment.

- **Schedule of Assessments for Cycle 9 onwards**

	Cycle 9 onwards			Final Study Visit[6]	Long-term Follow Up
	Day 22/1[5]	Dosing days	Weekly contact		
ECOG PS	X			X	
Brief physical examination[1]	X			X	
Vital signs[2]	X			X	
ECG (resting 12-lead)	X				
Clinical chemistry*	X			X	
Haematology	X			X	
Coagulation	X				
Urinalysis*	X				
Tumour assessment (radiological)[3]	X[3]			X[3]	
Tumour assessment (serum marker)[3]	X			X	
Immunogenicity	X			X	
Biomarker/PharmD assessment (biopsy)[4]	X				
Adverse events	X		X	X	
Concomitant medication	X		X	X	
ALM201 administration		X			
Long-term follow up[7]					X

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to ALM201 administration, unless specified otherwise.
- Additional assessments may be conducted as clinically indicated.
- (X) denotes an assessment not applicable to all patients.
- A tolerance of +/-1 day will be permitted for all study visits and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

* ***female patients, if fertile, will require a serum pregnancy test at Screening and urine pregnancy on Day 1 of each cycle***

Assessment Specific

1. Symptom-directed physical examination. Weight will be recorded on Day 1 of each cycle.

2. On each hospital administration day, vital signs (heart rate, BP, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after the ALM201 injection. Patient status will be monitored during ALM201 administration and repeat vital signs will be taken if needed.

3. CT or MRI performed at Screening and up to 7 days prior to start of every 4 cycles. Note that where there is a rationale for assessment of bone, these assessments will be performed as part of the CT assessment and not require additional radiological bone scan assessment.

   Other informative markers e.g. CA-125, PSA, photographs of melanoma skin lesions, may be taken as appropriate on Day 1 of each cycle.

   Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per appropriate response assessment guidelines. Any requirement for confirmatory scans will typically be performed at the next protocolled assessment time point. Other assessments e.g. whole body MRI or PET, are not protocol mandated, but may be performed as clinically indicated and at request of Investigator.

4. A post-treatment biopsy should be taken where possible if the patient has disease progression.

5. Day 22 of Cycle 9, 10, 11, 12, etc is Day 1 of Cycle 10, 11, 12, 13, etc.

6. The Final Study Visit should be performed 30 +/-3 days after the last dose of ALM201 to enable a final safety assessment.

7. Those patients who do not have disease progression at the Final Study Visit will be contacted every 8 weeks for up to 2 years (approximately) to check their status and commencement of their next anticancer treatment.

3.4 Permitted and Restricted Concomitant Medications/Treatments

All prescription, non-prescription, or over-the-counter medications including herbal remedies, dietary and nutritional supplements and complementary and alternative therapies given to, or taken by the patient at study entry (including Screening) and during the study must be clearly documented on the case report form (CRF).

Any medication considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator(s).

For treatment of DLT or any other clinically significant events, any available standard therapy may be used as required.

Prohibited treatments are summarized below:

- other antineoplastic agents;
- concurrent radiation treatment will be permitted during this study for symptom control;
- other investigational medicinal products.

3.5 Study Analysis Populations

Enrolled Patients: All patients who enroll in the trial.
Efficacy Population: All patients with at least one post-baseline tumour response assessment
Safety Population: All patients who receive at least one dose of study drug.

3.6 Withdrawn Patients

3.6.1 Patient Withdrawal or Discontinuation

Patients may withdraw from the study at any time without stating a reason and without prejudice to further treatment. A Final Study Visit should be performed 30 +/-3 days after the last dose of ALM201 to enable follow up safety assessments and further tumour assessment where required.

The Investigator may withdraw a patient from the study and discontinue study treatment and assessments at any time. Example reasons for discontinuing a patient from this study are:

- Disease progression.
- The patient experiences a toxicity, including those necessitating a dose delay of >14 days (See Protocol Section 4.2.1), where the re-introduction of ALM201 (including a dose reduction of ALM201), is not considered suitable. Exceptions may be considered where the toxicity is not considered to be ALM201 treatment-related.

- Other toxicities or events, unrelated to ALM201, that would, in the Investigator's opinion, prevent the patient from continuing on this trial.
- Protocol non-compliance. (All documentation concerning the patient must be as complete as possible. Withdrawals due to non-attendance of study visits must be followed-up by the Investigator to obtain the reason for where possible).
- Patient withdraws consent to participate in the study.
- Patient becomes pregnant (see Protocol, section 7.4.3)

The Sponsor reserves the right to request the withdrawal of a patient due to protocol violation or other significant reason. Patients who experience a toxicity event which qualifies as a DLT, may continue to receive ALM201 if considered safe to do so and where continued treatment is considered by the Investigator to be in the patient's best interests. The decision to continue treatment will be reviewed by the CRC (See Protocol Section 8.1) and will involve an adjustment (de-escalation) in dose or dose schedule.

3.6.2 Replacement of Non-evaluable Patients

In Part 1, patients will be replaced if they are not considered evaluable for DLT during Cycle 1. As a general rule during Part 1, patients will be considered evaluable for DLT during Cycle 1 if they receive at least 80% (i.e. 12 of 15 planned doses) of their intended dose, unless this is due to ALM201-related toxicity. However, this will be reviewed by the CRC on a case-by-case basis. For example, based on safety and PK data available, the CRC may agree that on a weekday dosing schedule, missing 1 dose per week on the 21-day dosing cycle is acceptable; whereas, missing 3 consecutive doses is not. Furthermore, the ability to evaluate a patient who misses more than 80% of their intended dose due to toxicity considered to be related to ALM201, but which is not ultimately classed as a DLT, will be reviewed on a case-by-case basis. Patients who withdraw from the study or discontinue treatment after completion of the first treatment cycle will not be replaced.

3.7 Sample Size

No formal sample size calculation was performed.

4 Statistical Methodology

4.1 Analysis Conventions

This section details general conventions to be used for the statistical analyses. Departures from these general conventions may be given in the specific detailed sections of this analysis plan. All data were collected using electronic case report forms (eCRFs).

- For all analyses, each dose level and overall will be summarized using descriptive summary statistics. Each treatment group will have a cohort number and data will be summarized in all tables, listings, and figures by treatment or cohort number. No statistical comparison of dose levels will be performed.

- Summary statistics will consist of the number and percentage for categorical variables, and the number of observations (n), mean, standard deviation (Sd), minimum, median, and maximum values for continuous variables. When the standard deviation cannot be calculated, a hyphen (-) will be used.

- All mean and median values will be formatted to one more decimal place than the measured value on the eCRF. Standard deviation values will be formatted to two more decimal places than the measured value on the eCRF. Minimum and maximum values will be presented with the same number of decimal places as the measured value on the eCRF.

- The number and percentages will be presented in the form XX (XX) where the percentage is in the parentheses. Unless otherwise specified, the denominator for percentages will be the number of patients in a given dose level within the analysis population of interest.

- All summary tables will include the analysis set sample size (i.e., number of patients).

- Baseline is defined as the last planned assessment before the first administration of study drug, unless otherwise specified. Typically this will be the Cycle 1 Day.

- Change from baseline will be calculated as follows:

  Change from baseline = Post-baseline value – baseline value.

- Age will be calculated as the integer: (Date of informed consent – date of birth)/365.25, rounded down to the nearest integer.

- Duration of time on study drug (days) = Date of last injection – date of first injection+1.

- Date and time variables will be formatted as DDMMMYYYY hh:mm for presentation.

- Summary tables with present data from scheduled assessments; listings will include all data, sorted by date.

- Tables, figures, and listings will be presented in landscape orientation.

- SAS® Version 9.4 or higher will be the statistical software package used for all data analysis.

- AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0.

- Prior cancer therapies and prior and concomitant medications will be coded using the WHO Drug dictionary version March 2014.

- No imputation of values for missing data will be performed, unless otherwise stated.

4.2 Disposition of Patients

Patient disposition will be summarized with the frequency and percentage of the following items: patients who enrolled (i.e., All Patients), patients who received at least one dose of study drug (i.e., Safety Population), patients who received at least one dose of study drug and completed at least one post-baseline response evaluation (i.e., Efficacy Population), the number of patients dosed at each cycle, patients who discontinued the study and the reasons for discontinuation.

A summary of protocol deviations will be presented. Protocol deviations are defined in Insight as:

- Eligibility
- ICF Issue
- IP Non-compliance
- IP Dispensing Error
- Assessment not performed per protocol
- Failure to adhere to visit schedule
- Other

Patient disposition, protocol deviations, and eligibility criteria (including inclusion/exclusion) will be presented in data listings.

4.3 Baseline and Demographic Characteristics

4.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics data will be summarized for all patients in the Safety population. Summary statistics will be calculated for race, ethnicity, gender, age, height (cm), weight (kg), left ventrical ejection fraction (LVEF) and Eastern Cooperative Oncology Group (ECOG) performance status at screening, as well as female reproductive status. Age will be

summarized as a continuous and categorical variable (≤ 55 years and > 55 years). All demographic and baseline data will be presented in data listings.

4.3.2 General Medical History

General medical history will be coded using MedDRA Version 17.0 system organ class (SOC) and preferred term (PT). It will be summarized, sorted by alphabetical order of SOC and preferred term. For the table summary, a patient will only be presented once for each level of summarization. Medical history will be presented in a data listing.

4.3.3 Cancer History

Time from date of initial cancer diagnosis to study entry (i.e., informed consent date) (months) and disease-specific characteristics of primary tumour, such as histology and tumour stage will be summarized.

Prior cancer therapies by number of previous regimens, duration of therapy, type of agent (chemo, immunotherapies, hormonal therapy, monoclonal therapy, radiation therapy and others), WHO ATC Level II drug class, and WHO preferred term, reason for administration, best response on therapy, and reason for discontinuation. For radiotherapies, field of radiation and estimated radiation dose will be summarized as well. All cancer history and prior cancer therapies will be presented in data listings.

4.3.4 Prior and Concomitant Medication and Ancillary Procedures

All prescription, non-prescription, or over-the-counter medications including herbal remedies, dietary and nutritional supplements and complementary and alternative therapies will be coded using the WHO Drug dictionary version March 2014 and classified into the default ATC code provided by the system.

A prior medication is defined as any medication started and stopped prior to the first administration of study drug. Concomitant medications are those taken on or after the first dose of study drug.

The incidence of concomitant medications by WHO ATC level II drug class and preferred term will be summarized and presented in alphabetical order of ATC level and preferred term for the Safety population. For the table summary, a patient will only be presented once for each level of summarization.

All medications (prior and concomitant) and any ancillary procedures will be presented in a data listing.

4.4 Exposure

Summary of exposure will include the total number of days on study medication and total dose received, and, by cycle, the location sites of injection, the total amount injected per visit and dose modification details. All study drug exposure information will be presented in a listing.

4.5 Efficacy / Primary and Secondary Analysis

As this is a phase 1 study, the extent of efficacy data is expected to be limited. However, a summary of Clinical benefit, by RECIST Version 1.1 from patients with evaluable disease will be generated. The summary will include the number and percent of patients, overall and by cohort with:

- Complete response (CR)
- Partial Response (PR)
- Overall Response (CR+PR)
- Stable Disease (SD)
- Disease Control Rate (SD+CR+PR)
- Progressive Disease (PD)
- Not Evaluable

Listings detailing the target, non-target, overall response assessments reported, and survival follow-up will be presented.

4.6 Pharmacokinetic Analysis

This analysis will be described in a separate document and the results presented in a separate document as well.

4.7 Analyses of Safety and Tolerability

All safety analysis will be performed on Safety Population.

4.7.1 Adverse Events

Adverse events will be summarized in terms of treatment-emergent adverse events (TEAEs) where treatment-emergent is defined as any AE that occurs after administration of the first dose of study drug and through 28 days after the last dose of study drug, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered study drug-related by the Investigator. Treatment-related TEAEs include those events considered by the investigator to be possibly, probably, or definitely related to study drug.

Adverse Events will be coded using MedDRA version 17.0 and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The incidence of TEAEs will be summarized by MedDRA System Organ Class (SOC), Preferred Term (PT) and NCI CTCAE grade. Tables summarizing the incidence of TEAEs will be generated for each of the following:

- Treatment Emergent AE Overview;
- All TEAEs by SOC and PT;
- TEAE by SOC, PT, and CTCAE Grade
- Treatment-Related TEAEs by SOC and PT;

- Treatment-Related TEAEs by SOC, PT and CTCAE grade;
- Treatment Emergent Serious Adverse Events by SOC and PT;
- Treatment Emergent Serious Adverse Events by SOC, PT and CTCAE grade;
- Treatment-Related Treatment Emergent Serious AEs by SOC and PT;
- Treatment-Related Treatment Emergent Serious Adverse Events by SOC, PT and CTCAE grade;
- Treatment-Emergent Adverse Events ≥ Grade 3 by SOC and PT
- Treatment-Related Treatment-Emergent Adverse Events ≥ Grade 3 by SOC and PT
- TEAEs leading to discontinuation of study drug by SOC and PT
- TEAEs leading to modification/interruption of study drug by SOC and PT
- Dose Limiting Toxicities by SOC and PT
- Fatal TEAEs by SOC and PT

If a patient experiences multiple episodes of the same event, the patient will only be counted once for that particular event. In the case of partially missing AE start dates, all available date information will be used to determine whether or not the AE is treatment-emergent. Adverse events with completely missing start dates will be considered to be treatment-emergent unless the stop date is known to be prior to the first administration of the study drug.

For tables that are presented by maximum grade, if a patient experiences multiple episodes of the same event, the event with the maximum grade will be used.

For tables that are presented by strongest relationship, if a patient experiences multiple episodes of the same event, the event with the strongest relationship to study drug will be used.

Deaths, serious adverse events (SAEs), and AEs resulting in study drug discontinuation also will be tabulated. The AE summaries will be presented in alphabetical order of SOC and preferred term.

All AEs, including treatment-emergent and non-treatment-emergent AEs, will be presented in data listings.

4.7.2 Laboratory Measurements

Scheduled clinical chemistry, hematology, coagulation, urinalysis and tumour biomarker, and other laboratory assessments will be collected and analyzed according to the study center's standard procedure. The laboratory assessments collected will be the following:

Clinical chemistry	*Haematology, including coagulation screen*
Calcium	Red cell count
Total protein	Hemoglobin
Albumin	Hematocrit

Clinical chemistry	*Haematology, including coagulation screen*
Total bilirubin	Absolute reticulocyte count
Alanine transaminase (ALT, SGPT)	Platelet count
Aspartate transaminase (AST, SGOT)	White blood cells
Alkaline phosphatase	Leucocyte differential count (% & absolute)
Glucose (random)	International normalized ratio or prothrombin time
Sodium	Activated partial thromboplastin time
Potassium	
Bicarbonate	
Chloride	
Magnesium	
Urea	
Creatinine	
Phosphate	
Uric acid	
Pregnancy test as required (Screening)	

Urinalysis
Glucose*
Protein*
Bilirubin*
Ketones*
Blood*
pH
Specific gravity & Microscopic examination when indicated
Pregnancy test as required

* Assessed categorically only

Creatinine clearance should be calculated using the Cockroft-Gault Formula, which is given below:

$$\textbf{Males:}\quad \frac{1.25 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (µmol/l)}}$$

$$\textbf{Females:}\quad \frac{1.05 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (µmol/l)}}$$

Cockroft DGM, 1976[iii]

Lab values will be expressed in SI units. Any lab data collected from local labs that are nont in SI units will be converted in the analysis dataset to SI units prior to summarization. Actual and change from baseline summary statistics will be presented at each scheduled time point of the study for each lab parameter. Laboratory parameters with categorical results will be summarized with the number and percentage of patients. Repeat and unscheduled measurements will not be summarized; however, they will be in the data listings.

Shift tables from baseline result to worst post-baseline result will be generated. In the shift tables, results will be categorized as low, normal, high, including low clinically significant and high clinically significant when available. If a patient has both low and high post-baseline values, the summary table will display the result with the greatest absolute departure from the normal limits for that parameter. The denominators for the percentages will be the number of patients with non-missing data at both the baseline and any post-baseline time point for a parameter.

4.7.3 Physical Examinations and Pregnancy Tests

All PE results will be presented in data listings. No pregnancy testing was conducted during this study.

4.7.4 Eastern Clinical Oncology Group Performance Status (ECOG PS)

Frequencies and percentage of patients with each ECOG performance status (PS) will be summarized as a categorical variable by cycle and worst status overall. All ECOG PS will be presented in a data listing.

4.7.5 12-Lead Electrocardiogram

The actual ECG measurements at each study evaluation time point along with the corresponding change from baseline calculation will be summarized for heart rate, PR, QRS, QT and QTc calculated using Fridericia's correction.

Overall ECG interpretations will be summarized using a shift table from baseline to the worst post-baseline interpretation. ECG interpretations will be reported as normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS).

The denominators for the percentages will be the number of patients with non-missing data at both the baseline and any post-baseline visit. Additionally, the number and percentage of patients with elevated QT interval corrected for Fridericia's formula (QTcF) (> 450 and > 470) will be summarized by visit.

All 12-Lead ECG data will be presented in a data listing.

4.7.6 Vital Signs

The actual vital signs measurements at each scheduled time point along with the corresponding change from baseline calculations will be summarized for systolic/diastolic blood pressure (mmHg), pulse (beats/min), temperature (°C), respiratory rate (breaths/min), and weight (kg).

All vital signs will be presented in a data listing.

4.7.7 Echocardiogram

Listings of the left ventricular ejection fraction (LVEF) obtained by echocardiogram or MUGA, at screening, will be presented in listings.

4.7.8 Immunogenicity and Pharmacodynamic Samples

Listings of all samples collected to assess biomarker and PharmD activity will be presented.

- Ascites Samples
- Blood Samples for Biomarkers
- Biopsy Samples Biomarkers
- Immunogenicity Samples
- Serum Tumour Marker Samples

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.1.3 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible, data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by treatment group, patient and visit and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

6 References

Eisenhauer EA, Therasse P, Bogaerts J, et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 228-247. (http://www.eortc.be/recist/documents/RECISTGuidelines.pdf)

Rustin GJS, Vergote I, Eisenhauer E, et al. (2011) Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 21: 419-423

Hinnen P and Eskens F A L M. (2007)Vascular disrupting agents in clinical development. Br J Cancer. Apr 23, 96(8): 1159–1165.

Eskander RN and Tewari KS (2014) Incorporation of anti-angiogenesis therapy in the management of advanced ovarian carcinoma – Mechanistics, review of phase III randomized clinical trials, and regulatory implications Gynecologic Oncology 132: 496-505

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Cockroft DGM. (1976) Prediction of creatinine clearance from serum creatinine. Nephron. 16:31-41.

[i] Eisenhauer EA, Therasse P, Bogaerts J, et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 228-247. (http://www.eortc.be/recist/documents/RECISTGuidelines.pdf)

[ii] Rustin GJS, Vergote I, Eisenhauer E, et al. (2011) Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 21: 419-423

[iii] Cockroft DGM. (1976) Prediction of creatinine clearance from serum creatinine. Nephron. 16:31-41.