CLINICAL STUDY PROTOCOL SYNOPSIS

A phase I open-label multicentre dose-escalation study of subcutaneous ALM201 in patients with advanced ovarian cancer and other solid tumours

Study Protocol:	ALM201/0001
Study Drug(s):	ALM201
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PROTOCOL SYNOPSIS

Protocol No:
ALM201/0001

Study Title:
A phase I open-label multicentre dose-escalation study of subcutaneous ALM201 in patients with advanced ovarian cancer and other solid tumours.

Investigational Product:
ALM201

Phase of Development:
1

No of Sites:
For dose escalation (Part 1): 3 UK sites

For further assessment of the Maximum Tolerated Dose (MTD), Maximum Feasible Dose (MFD) and/or Biologically Active Dose (BAD) in Part 2: up to 5 additional UK sites may be added in order to ensure there is an acceptable enrolment rate.

No of Patients:
The final sample size will depend on the number of Dose Limiting Toxicities (DLTs) observed at each dose level and any Cohort Review Committee (CRC) decision to assess an alternative treatment schedule in Part 1, plus the number of enrichment cohorts assessed at the MTD, MFD and/or BAD in Part 2.

Up to 36 evaluable patients would be anticipated for Part 1 based on a conservative estimate of enrolling a maximum of 36 patients across 6 dose escalation cohorts. Up to an additional 12 patients may also be enrolled to Part 1 for the assessment of alternative dose schedule(s).

No more than 36 evaluable patients will be enrolled for Part 2. This upper limit is based on an estimate of up to 12 patients being evaluated at 3 dose levels of interest.

Study Objectives and Endpoints:
The primary objectives of this study are to characterize the safety and tolerability of ALM201 and to identify a recommended phase 2 dose and schedule of administration of ALM201 in patients with advanced ovarian cancer.

Objective	Endpoint(s) (Assessment)
Primary:	
• To characterise the safety and tolerability of ALM201 (Parts 1 and 2)	• Ongoing evaluation of AEs during treatment and follow up; evaluation of DLT during Cycle 1 (Part 1 only)
• To identify a recommended phase 2 dose and schedule of ALM201 (Part 2 only)	• Safety, PK, PD and tumour response assessments
Secondary:	
• To establish the pharmacokinetic profile of ALM201	• Assessment of pharmacokinetic variables (including C_{max}, C_{min}, AUC)
• To assess anti-tumour activity	• Tumour response assessment by RECIST 1.1(Eisenhauer et al, 2009[i]) and/or other relevant response assessments for tumour types enrolled
• To assess anti-tumour activity in a biomarker-enriched group of patients with advanced ovarian cancer (Part 2 only)	• Tumour response assessment by RECIST 1.1(Eisenhauer et al, 2009[i])
Exploratory:	
• To assess relevant tumour biomarkers and the pharmacodynamic activity of ALM201	• Assessment of relevant tumour biomarkers and markers of ALM201 activity o 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 o in blood e.g. RASSF1 methylation, and other relevant or exploratory biomarkers appropriate for tumour type o in ascites (Part 2 only) e.g. stem cell count, and other relevant or exploratory biomarkers appropriate for ovarian cancer

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 PD data as available. Every new dose cohort will be evaluated for the occurrence of a DLT during Cycle 1 of treatment (Section 4.2.1).

Accelerated enrolment followed by a 3+3 design

Part 1 of the study will commence with an accelerated dose escalation schedule and enrol 1 patient into a cohort with follow up for adverse events (AEs) and DLT during Cycle 1. The CRC will meet as soon as possible once the final study visit in Cycle 1 has taken place in each cohort to review patient safety data to the end of Cycle 1. Where there are no safety concerns, a 100% dose escalation step will be permitted for the next cohort. Where the CRC suspects that drug-related events have occurred that could progress to DLT upon further dose escalation e.g. clinically significant NCI (National Cancer Institute) CTCAE (Common Terminology Criteria for Adverse Events) Grade 2 events considered to be related to ALM201, they will confirm that future cohorts must enrol at least 3 patients in order to more thoroughly evaluate potential drug-related adverse events. The CRC may also advise that the current dose level under evaluation be expanded to 3 patients prior to further dose escalation in order to help inform the next dose escalation step. Dose escalation of 3-patient cohorts will proceed according to the scheme presented in Section 4.2. Note that there will always be stagger of at least 1 week between dosing the first and subsequent patients in a new dose cohort. The CRC may request there be a further or prolonged stagger introduced during the trial, depending on the nature of adverse events observed to date.

Dose Limiting Toxicity

The CRC will agree on the next appropriate dose escalation step for each cohort primarily based on DLT evaluation during Cycle 1 of the current cohort. Only events occurring during the first cycle of treatment will be considered for DLT determination; however, there will be on-going evaluation of AEs in subsequent treatment cycles during the cohort review process. Clinically significant events thought to be potentially related to ALM201, or trends in adverse events seen in subsequent cycles will be taken into account when considering future dose escalation steps and dose administration schedules.

Upon occurrence of the first DLT in any cohort, additional patients will be added to that cohort so that up to a total of 6 can be evaluated. Once expansion to a 6-patient cohort has been recommended due to the identification of a DLT, escalation to the next 3-patient cohort will only occur when all patients in the expanded cohort have completed their first cycle of ALM201 and no more than 1 DLT has occurred. If 2 or more DLTs occur in an expanded cohort, DLT is established and the next lower dose level will be declared the MTD.

The highest dose where $\leq$ 1 DLT is seen in 3 or 6 patients will be termed the MTD. Note that intermediate dose levels may be explored below the dose level where $\geq$2 DLTs were seen, in order to identify the maximum dose which may be adequately tolerated. The 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 (Section 6). Should this dose be reached without the need to de-escalate due to DLT, it will be termed the MFD.

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

Safety evaluations will be conducted weekly during each treatment cycle, with DLT assessed during Cycle 1 only. All events and suspected DLTs will be graded according to the CTCAE v4.03.

A DLT is defined as a Grade 3 or 4 AE that, in the opinion of the CRC, is likely to be related to ALM201 and represents a clinically significant hazard to the subject. Qualifying DLT events must be considered to be clinically relevant e.g. in duration, apparent reversibility, required management, and upon consideration of the patient's medical history and/or concomitant medications. DLT events must also be evaluated in terms of what is considered to be an appropriate next escalation step: in the case where the CRC agree that an escalation step of approximately 33% or lower is merited, the toxicity of concern should be declared a DLT.

Examples of exceptions that will be considered by the CRC are as follows:

- Grade 3 or 4 laboratory abnormalities, which resolve spontaneously or can be corrected with appropriate treatment (such as electrolytes) e.g. an event returns to baseline or to Grade 1 or less prior to the next administration);
- Symptomatic adverse events, such as nausea, vomiting and diarrhea, if they can be reduced to less than Grade 3 with standard supportive measures, such as anti-emetics and anti-diarrhoeals within 72 hours.

In order to be evaluable for DLT assessment, a patient must have received at least 80% of their scheduled doses (e.g. 12 of the 15), unless this lack of compliance is due to ALM201-related toxicity. DLT events must therefore be considered in terms of inability to administer the planned Cycle 1 dose administration schedule, and in such cases a dose delay of more than 14 days due to a toxicity event considered related to ALM201 will be considered to be a DLT (Section 4.4.1).

Part 1: Dose Escalation

In the absence of DLT or suggestion of ALM201-related adverse events which would lead to more cautious dose escalation, the following table presents a hypothesised dose escalation plan:

Cohort	Escalation Step	Dose level
1 (Starting Dose)	-	10 mg
2	(2X starting dose)	20 mg
3	(4X starting dose)	40 mg
4	(8X starting dose)	80 mg
5	(16X starting dose)	160 mg
6 (MFD)	(30X starting dose)	300 mg

The dose may be doubled in sequential cohorts where the CRC consider it appropriate to do so, based on on-going evaluation of DLTs and adverse event data. Dose escalation decisions will also take available PK and pharmacodynamic (PD) data into consideration.

In the case where a potentially significant toxicity occurs, or a trend in toxicities is seen, considered to be related to treatment with ALM201 and potentially a precursor to a clinically significant toxicity event, subsequent dose escalation steps will be more conservative and will not exceed 50% of the previous dose. This restriction may be reversed where there is no suggestion of potentially clinical significant toxicity in subsequent cohort(s). In the case where a single DLT event is confirmed in an expanded cohort, the next dose escalation step will not exceed 33% of the previous dose. However, where there are no further events seen in the next cohort; the CRC may allow future dose escalation steps of up to 50%.

Note that the CRC may also recommend that an MTD, MFD or BAD be assessed in a cohort of 6 patients in Part 1 where only 3 patients have received this dose level to date, prior to recommending the enrolment of an enrichment cohort to receive this dose level in Part 2.

Cohort Review Committee

All dose escalation decisions will be made by a CRC who shall convene to review all available AE, PK, PD and relevant patient data (Section 8.1). Patients in Part 1 will be eligible for DLT evaluation if they have received 80% e.g. 12 of their 15 scheduled doses, during Cycle 1. The CRC will be composed of the trial investigators, a patient representative, sponsor representative(s) and the study Medical Monitor. Additional experts may be invited to support the review of the data as required e.g. a pharmacokineticist. The Contract Research Organisation (CRO) responsible for managing and monitoring the trial will also support the preparation and conduct of the CRC meetings and may attend such meetings. All data reviewed, CRC discussions and agreed dose escalation recommendations will be minuted. The composition of the CRC and the data review processes to be followed by the committee will be fully described in a CRC Charter.

Based on on-going safety, PK and PD data evaluation, the CRC may also recommend dose de-escalation steps or adjustments in the dose administration schedule of ALM201. Upon review of available safety, PK and PD data, the CRC may recommend that an alternative dose administration schedule of ALM201 be explored. Less intense dose administration schedules will be permitted as long as the unit dose does not exceed the next permitted escalation step. Given the starting dose administration schedule is week-day dosing i.e. D1-5, D8-12, D15-19, on a 21 day cycle, a more dose intense dosing schedule is unlikely. However, should the CRC consider this reasonable to explore, the same dose escalation rules will apply and pharmacokinetic modelling, in conjunction with the safety data obtained to date, will be used to inform the appropriate dose level for a more dose intense dose schedule.

Note that the MTD or MFD need not be confirmed for the original dose administration schedule prior to the CRC recommending the investigation of an alternative dose administration schedule. Multiple dose escalation tracks may be followed if more than one dose schedule is considered relevant to explore i.e. the CRC may recommend that the alternative dose administration schedule

replaces a schedule or is explored in addition to another schedule, as long as dose escalation rules are not exceeded.

Duration of treatment

The main study will permit a maximum of 8 three-weekly treatment cycles (or approximately 6 months of treatment). Patients who are seen to potentially be benefiting from treatment i.e. patients whose disease has not progressed and who have not been withdrawn from therapy due to toxicity, will be eligible to continue to receive additional cycles of ALM201 where this is recommended by their study physician, subject to availability of ALM201. Such patients will continue to be followed up for compliance, toxicity and continued response (Schedule of Study Assessments).

Part 2: Enrichment at MTD, MFD and/or BAD

Once an MTD, MFD and/or BAD has been established for a given dose and schedule in Part 1, Part 2 may commence. Part 2 will involve up to an additional 36 patients with advanced ovarian cancer. During Part 2 of the study there will be on-going evaluation of safety and the opportunity to obtain preliminary anti-tumour activity at each dose level selected in the ovarian cancer population. The only dose adjustments permitted in Part 2 will be dose de-escalations (based on a de-escalation of the unit dose or a less frequent administration schedule of the maximum unit dose). Such decisions will be driven by each patient's tolerability of ALM201. Where possible, such dose reductions should be made by the CRC who can convene on an ad-hoc basis to advise on the appropriate dose adjustment; however, the investigator may implement a dose reduction prior to CRC review in the interest of patient safety.

Study Assessments:

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.

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. For all administrations in hospital, the patients must wait for at least 60 minutes from the time of the ALM201 injection for observation and repeat vital signs. These precautions are in case of emergent evidence of immunogenicity in Cycle 1, and at other times after the weekend break in dosing.

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. 2011[ii]), 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.

All patients will be asked to provide consent for access to archived tumour tissue where available, and where possible, fresh biopsies will be taken pre-dose and again during the study where the patient has a documented tumour response and/or at the point of disease progression to allow for potential biomarker and pharmacodynamic assessment. In Part 2, access to a tumour biopsy sample will be required to confirm each patient's eligibility for the study (see Inclusion Criterion 2). A fresh biopsy will be preferable for this purpose; however, where it is not possible to obtain this, confirmation of the angiogenesis signature may be performed on archived tumour tissue during Screening. In Part 2, there will also be additional biomarker/PD assessments in blood and ascites. In both parts of the study, any remaining samples obtained for biomarker/PD assessment will be retained for potential future analysis.

Patients will be withdrawn from the study at the point of receiving their last dose of ALM201. However, all patients will be asked to participate in a protocolled follow up assessment 4 weeks after their last dose for safety assessments. Furthermore, patients will continue to be followed up either in the study clinic or by telephone contact every 8 weeks (Schedule of Study Assessments) for up to approximately a 2 year period, to check their disease (survival) status and commencement of next anti-cancer treatment.

Inclusion/Exclusion Criteria:

Part 1 will enrol patients with advanced solid tumours in whom treatment with an anti-angiogenic agent is appropriate. Part 2 will enrol patients with ovarian cancer, screened using an angiogenesis gene signature, that have failed to respond to, or have relapsed following standard therapy.

Inclusion Criteria

(i) Part 1 Specific Inclusion Criterion

1. Patients with histologically and/or cytologically confirmed advanced solid tumour for whom no standard effective therapy is available or felt likely to be of limited efficacy and in whom a rationale for use of an anti-angiogenic treatment approach exists. Note: *Previous use of anti-angiogenic therapy is allowed if tolerated*

(ii) Part 2 Specific Inclusion Criterion

2. Patients with advanced ovarian cancer, who are intolerant of or whose tumour is resistant to platinums and who have failed to respond to, or have relapsed following, standard therapy and whose tumour has a proangiogenic profile as assessed by the angiogenesis gene signature test. Note: *Previous use of anti-angiogenic therapy is allowed if tolerated.*

(iii) General Inclusion Criteria for all Patients

3. Adult patients defined by age ≥16 years at time of consent.

4. Evaluable disease, either measurable on imaging, or with informative tumour marker(s), as assessed by RECIST 1.1 (Eisenhauer et al, 2009[i]) or other relevant response assessment criteria for tumour type.

5. Recovery from previous treatment to baseline or CTCAE ≤ Grade 1, as determined by CTCAE v4.03 criteria (Appendix B), of reversible toxicities related to prior treatment, with the exception of alopecia, lymphopenia, other non-clinically significant adverse events; recovery from previous radiotherapy other than residual cutaneous effects or stable < Grade 2 gastrointestinal toxicity; complete recovery from surgery other than stable < Grade 2 toxicity.

6. Eastern Collaborative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 (Appendix A).

7. Laboratory values at Screening:

   - Absolute neutrophil count ≥1.5 x 10^9/L without colony stimulating factor support;
   - Platelets ≥100 x 10^9/L;
   - Haemoglobin ≥9 g/dL (not transfusion dependent);
   - Total bilirubin <1.5 times the upper limit of normal (ULN) (unless due to Gilbert's syndrome where it should be ≤ 2.5 x ULN);
   - AST (SGOT) ≤2.5 times the ULN; ALT (SGPT) ≤2.5 times the ULN; ≤5 x ULN for patients with advanced solid tumours with liver metastases; patients with confirmed bony metastases will be permitted on study with isolated elevations in ALP < 5 times the ULN;
   - Serum creatinine ≤ 1.5 x ULN or estimated glomerular filtration rate (GFR) of >50 mL/min based on the Cockcroft-Gault formula (Appendix D);
   - Normal coagulation (elevated INR, prothrombin time or APTT ≤ 1.3 x ULN range acceptable);
   - Urine protein ≤2+ (as measured by dipstick).

8. Negative urine or blood human chorionic gonadotropin (hCG) test during Screening and within 7 days of Cycle 1, Day 1 in women of childbearing potential (defined as women ≤ 50 years of age or history of amenorrhea for ≤ 12 months prior to study entry). Sexually active male and female patients of childbearing potential must agree to use an effective method of birth control e.g. barrier methods with spermicides, oral or parenteral contraceptives and/or intrauterine devices, during the entire duration of the study and for 6 months after final administration of ALM201. Note that sterility in female patients must be confirmed in the patients' medical records and can be defined as any of the following: surgical hysterectomy with bilateral oophorectomy, natural menopause with menses >1 year ago; radiation induced oophorectomy with last menses >1 year ago; chemotherapy induced menopause with 1 year interval since last menses.

9. Ability to give written, informed consent prior to any study-specific Screening procedures, with the understanding that the consent may be withdrawn by the patient at any time without prejudice.

10. Patient is capable of understanding the protocol requirements, is willing and able to comply with the study protocol procedures, and has signed the informed consent document.

Exclusion Criteria for all Patients

1. History of inability to tolerate anti-angiogenic therapies e.g. increased blood pressure (BP), proteinuria, prior thromboembolic events.

2. Previous history of bowel obstruction, clinical evidence of gastro-intestinal obstruction, large burden of peritoneal disease or evidence of bowel involvement on computed tomography.

3. Patents has received:

   a) any chemotherapy regimens (including investigational agents) with delayed toxicity within 4 weeks (6 weeks for prior nitrosourea or mitomycin C) of Cycle 1, Day 1, or received chemotherapy regimens given continuously or on a weekly basis which have limited potential for delayed toxicity within 2 weeks of Cycle 1, Day 1.

   b) radiotherapy, immunotherapy or biological agents (includes investigational agents) within 4 weeks of Cycle 1, Day 1. Localised palliative radiotherapy is permitted for symptom control.

4. Documented, symptomatic or uncontrolled intracranial metastases or primary intracerebral tumours.

5. Cancer with leptomeningeal involvement.

6. On therapeutic anti-coagulation (aspirin dosing ≤100 mg per oral (PO) daily allowed).

7. Previous malignancy, except for non-basal-cell carcinoma of skin or carcinoma-in-situ of the uterine cervix, unless the tumour was treated with curative intent more than 2 years prior to study entry.

8. History of clinically significant cardiac condition, including uncontrolled hypertension (BP >140/90 mmHg, despite medical therapy); left ventricular systolic dysfunction (ejection fraction (<55 %) on echocardiography) with or without heart failure symptoms; history of an ischaemic cardiac event within 3 months of study entry (myocardial infarction, acute coronary syndrome); QT interval prolongation (QTcF, Fridericia's Correction of >450 ms on screening 12-lead ECG); clinically significant cardiac arrhythmia within 3 months of study entry. Note: *ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, atrial fibrillation without adequate heart rate control, atrial fibrillation with adequate heart rate control with or without medication or other treatment, are not an exclusion.*

9. Known human immunodeficiency virus positivity.

10. Active hepatitis B or C or other active liver disease (other than malignancy).

11. Any active, clinically significant, viral, bacterial, or systemic fungal infection within 4 weeks prior to Cycle 1, Day 1.

12. Any evidence of severe or uncontrolled systemic conditions or any other issues which make it undesirable for the patient to participate in the study or which could jeopardize compliance with the protocol.

Route of Administration, Dose Schedule and Duration:

ALM201 administered as a SC injection with a maximum administration volume of 1.0 mL per injection. Each 1 ml injection will contain 100 mg ALM201. A maximum of 3 x 1.0 mL injections may be given for any single dose, therefore the MFD will be 300 mg. The starting dose level of ALM201 is 10 mg given on Days 1-5, 8-12 and 15-19 of a 21-day cycle. The SC injection may be given in the abdomen, leg or arm following local administration guidelines including the use of premedication as required for local injection site reactions. The dose levels assessed in this study i.e. the dose and dosing administration schedule, may be adjusted following the study dose escalation rules, based on review of on-going evaluation of safety, PK and PD data generated during the study.

Statistical Methods:

There will be no formal statistical analysis in the dose-escalation phase this study. Results will be listed and summarised using descriptive statistics. In Part 2, response rate will be assessed and summarised and an exact 95% confidence interval (CI) calculated. Analyses will be performed on the whole population plus those who have and have not been previously exposed to anti-angiogenics and those who have and not been exposed to tubulin-targeting agents before entry to this trial.

SCHEDULE OF STUDY ASSESSMENTS

(i) 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/PD assessment (biopsy)[5]	X	X - up to 2 post-treatment samples																					
Biomarker/PD assessment (blood sample)[6]	X	X - up to 12 post-treatment samples																					
Biomarker/PD 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/PD evaluation. The study will encourage taking fresh biopsies for biomarker/PD 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/PD 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/PD 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.

(ii) Schedule of Study Assessments for Alternative Dose Schedules

	Screening	Cycle 1				Cycle 2 – 4			Cycle 5 – 8				Final Study Visit[11]	Long-term Follow Up
		Day				Day			Day					
	-28 to 0	1	2	Other dosing days	Weekly clinic visits	22/1[10]	Other dosing days	Weekly contact	22/1[10]	Other dosing days	Weekly contact	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	
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/PD assessment (biopsy)[5]	X	X – up to 2 post-treatment samples												
Biomarker/PD assessment (blood sample)[6]	X	X - up to 12 post-treatment samples												
Biomarker/PD 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/PD evaluation. The study will encourage taking fresh biopsies for biomarker/PD 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/PD 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/PD 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.

(iii) 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/PD 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.