ADVENCHEN LABORATORIES, LLC

INVESTIGATIONAL NEW DRUG PROTOCOL

AL3818 (ANLOTINIB HYDROCHOLORIDE)

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A Phase 1/2a Evaluation of the Safety and Efficacy of Adding AL3818, a Dual Receptor Tyrosine Kinase Inhibitor, to Standard Platinum-Based Chemotherapy in Subjects with Advanced or Recurrent Endometrial, Ovarian, Fallopian, or Primary Peritoneal or Cervical Carcinoma

SPONSOR:

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CONFIDENTIAL

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
A/G ratio	Albumin to globulin ratio
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
$AUC_{(0-inf)}$	Area under the curve to infinity
$AUC_{(0-t)}$	Area under the curve to the last measurable concentration
bFGF	Basic fibroblast growth factor
ß-hCG	Beta-human chorionic gonadotropin
BSA	Body surface area
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAM	Chorioallantoic membrane
CBC	Complete blood cell count
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CL	Total clearance
cm	Centimeter
C_{max}	Maximum serum concentration
CMP	Comprehensive metabolic panel
CMUVEC	Cynomolgus monkey derived umbilical vein endothelial cells

ABBREVIATION	DEFINITION
CNS	Central nervous system
CO_2	Carbon dioxide
CPN	Chronic progressive nephropathy
CRF	Case report form
CRU	Clinical research unit
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (v. 4.03)
dL	Deciliter
DLT	Dose limiting toxicity
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbant assay
EPC	Endothelial progenitor cell
FAK	Focal adhesion kinase
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice(s)
HDL	High-density lipoprotein
HNSTD	Highest Non-Significantly Toxic Dose
HUVEC	Human umbilical vein endothelial cell
ICH	International Conference on Harmonization
IND	Investigational New Drug

ABBREVIATION	DEFINITION
INR	International normalized ratio
IP	Intraperitoneal(ly)
IRB	Institutional Review Board
k_{10}	Rate constant for elimination from the central compartment
kg	Kilogram
K_{21} or K_{12}	Rate constant for intercompartmental transfer
L	Liter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOAEL	Lowest observed adverse effect level
λz	Elimination rate constant
m^2	Square meters
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum Feasible Dose
µg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
mM	Millimolar
MTD	Maximum tolerated dose
NaCl	Sodium chloride
NCI	National Cancer Institute
ng	Nanogram
nm	Nanometer
NOAEL	No observed adverse effect level

ABBREVIATION	DEFINITION
NSTD	Non-severely toxic dose
PBS	Phosphate buffered saline
PD	Pharmacodynamic(s)
pH	Hydrogen ion concentration
PK	Pharmacokinetic(s)
PT	Prothrombin time
q.s.	Quantum statis (sufficient quantity)
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SC	Subcutaneous(ly)
STD	Severely toxic dose
$t_{1/2}$	Elimination half-life
TBD	To be determined
ULN	Upper limit of normal
U.S.	United States (of America)
USP	United States Pharmacopeia
VEGF	Vascular endothelial growth factor
V_c	Volume of the central compartment
V_z	Volume of distribution
WBC	White blood cell count
WHODRL	World Health Organization Drug Dictionary

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INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Conference on Harmonisation Good Clinical Practice Guidelines E6 (ICH-GCP).

I will maintain accurate source documents from which data are transcribed onto case report forms and accurate drug accountability records that show the receipt and disposition of all study drugs.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB-approved Informed Consent Form is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event, regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in Section 13.2 of the protocol. I will notify the Sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

I will submit all protocol inclusion/exclusion violations to the medical monitor for approval prior to enrollment of the subject in the study.

I will allow the Sponsor, Advenchen Laboratories, LLC, Inc. and its agents, as well as the United States (U.S.) Food and Drug Administration (FDA) and other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (no later than 1 week).

This protocol contains information that is proprietary to Advenchen Laboratories, LLC, Inc. The information contained herein is provided for the purpose of conducting a clinical trial for Advenchen Laboratories, LLC, Inc.

The contents of this protocol may be disclosed to study personnel under your supervision and to your IRB/EC. The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of Advenchen Laboratories, LLC, Inc.

_____   _____

Investigator's Signature   Date

| **PROTOCOL SYNOPSIS** |

Study Title	A Phase 1/2a Evaluation of the Safety and Efficacy of adding AL3818, a dual receptor tyrosine kinase inhibitor, to standard platinum-based chemotherapy in subjects with advanced or recurrent endometrial, ovarian, fallopian tube, or primary peritoneal or cervical carcinoma (AL3818-US-002)
Phase	1/2a
Study Drug	AL3818 (Anlotinib Hydrochloride) Capsules
Study Population	Female subjects 18 years of age or older who have the following cancers: • Advanced or recurrent endometrial cancer subjects, • Advanced or recurrent ovarian, fallopian tube, or primary peritoneal carcinoma subjects, OR • Advanced or recurrent cervical carcinoma subjects who have progressed $\geq$ 6 months after the last cycle of first-line chemotherapy or $\geq$ 6 weeks after biologic maintenance therapy.

Objectives	**Part 1: Phase 1b Portion**
	Primary objective:
	• The primary objective of this study is to investigate the safety and tolerability of adding oral AL3818 to standard platinum-based chemotherapy with carboplatin and paclitaxel.
	• Determination of MTD in the study population.
	Part 2: Phase 2a Portion
	Primary objective:
	• To obtain data on objective response rates in subjects with advanced or recurrent endometrial, ovarian, fallopian tube, primary peritoneal, or cervical carcinoma treated with AL3818 given concurrently with carboplatin and paclitaxel chemotherapy and continued as maintenance treatment for up to 18 months after completion of chemotherapy.
	Secondary objectives:
	• To obtain data on overall survival (OS) rates in subjects with advanced or recurrent endometrial, ovarian, fallopian tube, primary peritoneal, or cervical carcinoma treated with AL3818.
	• Toxicity
	• Quality of Life (QoL)

| **Study Rationale** | Four (4) angiogenesis inhibitors have been approved in the U.S. in the past 2 years for the treatment of cancer: 1) sunitinib (Sutent®) for the treatment of gastrointestinal stromal tumors and renal cell carcinoma; 2) bevacizumab (Avastin®) for the treatment of metastatic colorectal carcinoma,non-small cell lung cancer, advanced cervix and platinum-resistant ovarian cancer; 3) sorafenib (Nexavar®) was approved for the treatment of renal and hepatic tumors. Bevacizumab and sunitinib, which interfere with VEGF/VEGF signaling pathways, have been associated with hemorrhagic events. In addition, bevacizumab has been associated with gastrointestinal perforations and wound healing complications, and sunitinib has been associated with left ventricular dysfunction, hypertension, and abnormal adrenal function. Sorafenib is known to cause severe gastrointestinal perforations and other side effects, cardiovascular side effects and dermatologic side effects. Other therapies that inhibit epidermal growth factor receptor (EGFR), such as cetuximab, a monoclonal antibody, have been associated with infusion reactions and cardiopulmonary arrest. Another EGFR, lupatinib (Tykerb®) for the treatment of metastatic breast cancer is associated with the potential to develop toxic hepatitis.

The induction of angiogenesis is a hallmark of metastatic cancers and their ability to sustain continued growth. Anti-angiogenic therapy has proven beneficial in multiple cancers, including ovarian cancer, predominantly by improving response rates in combination with chemotherapy and improving outcomes such as progression free survival (PFS). The dominant target in anti- angiogenesis therapy is vascular endothelial growth factor (VEGF) and its receptor [1]. Vascular endothelial growth factor (VEGF) plays a pivotal role in tumor angiogenesis, a process critical for tumor development, invasion, and metastasis [2].

Ovarian Cancer:

Ovarian cancer is the leading cause of death among gynecologic malignancies with an estimated 14,030 deaths in 2013 [3]. Patients with advanced stage disease at the time of diagnosis have a high risk for recurrence and less than 40 % of patients are cured. Platinum-based therapy is the mainstay of treatment for ovarian cancer; however, a major limitation to the use of these agents is the development of platinum-resistance. Unfortunately, recurrent disease is generally not curable, and response rates for second line chemotherapy are in the 15-20 % range. Since there is no known effective therapy for patients with ovarian cancer who have relapsed after or are refractory to two prior regimens, efforts in finding new targeted treatments for this population need to be pursued, though an incomplete understanding of the pathways driving neoplastic transformation and tumor growth has limited the expansion of efficient targeted therapies for patients with ovarian cancer. The induction of angiogenesis is a hallmark of metastatic cancers and their ability to sustain continued growth. Anti-angiogenic therapy has proven beneficial in multiple cancers, including ovarian cancer, predominantly by improving response rates in combination with chemotherapy and improving outcomes such as progression free survival (PFS). The dominant target in anti-angiogenesis therapy is vascular endothelial growth factor (VEGF) and its receptor. Vascular endothelial growth factor (VEGF) plays a pivotal role in tumor angiogenesis, a process critical for tumor development, invasion, and metastasis. Increased levels of VEGF are associated with poor prognosis and have been shown to be an independent predictor of survival in ovarian cancer [4, 5]. Thus, exploring the utility of a multi-kinase inhibitor with anti-angiogenic activity is reasonable in ovarian cancer. There have been number of studies of the FGF-FGFR family in ovarian cancer. PCR studies showed that the FGF3 gene was amplified in 20% of ovarian cancer samples and that this was significantly associated with FIGO stage but not with overall survival [6]. FGFR2 IIIb is |

Study Rationale (cont.)	expressed in 80 % of epithelial ovarian carcinomas, whereas FGF1 was only expressed in 20 % and 60 % of epithelial ovarian carcinomas, respectively [3]. Ovarian epithelial transformation is associated with the establishment of an autocrine circuit consisting of FGF3/7 and FGFR2IIIb. Inhibition of this axis at the cytokine or receptor level impacts on proliferation and platinum sensitivity in vitro and in vivo, thus highlighting FGFR2 and it cytokines, FGF3 and 7, as potential new targets for the treatment of ovarian cancer..
	Preclinical studies have demonstrated that mutant FGFR2 endometrial cell lines are highly sensitive to FGFR tyrosine kinase inhibitors.
	Standard treatment for ovarian cancer patients relapsing 6 or more months after first-line therapy is platinum-based usually involving carboplatin in combination with paclitaxel, liposomal doxorubicin or gemcitabine. Efforts to treat platinum-sensitive relapsed ovarian cancer are actively being explored. Combination therapy involving the addition of angiogenesis inhibitors to platinum-based chemotherapy is one way being explored to treat relapsed ovarian cancer. For instance, addition of cediranib to platinum-based chemotherapy involving carboplatin and paclitaxel was found to increase progression-free survival (PFS) and overall survival (OS) rates in the ICON 6 trials carried out in the UK [7, 8].
	Increased levels of VEGF are associated with poor prognosis and have been shown to be an independent predictor of survival in ovarian cancer [4, 9]. Blocking angiogenesis has been shown to be an effective strategy for controlling tumor growth in EOC. Angiogenesis appears to be an important factor in both th development and subsequent progression of EOC. [10, 11] Yoneda and colleagues demonstrated in a xenograft model of EOC that tumor growth rates were directly proportional to vascular density and that the development of malignant ascites, a feature associated with poor outcome in EOC, was associated with the expression of vascular endothelial growth factor. [12]
	In platinum-relapsed epithelial ovarian cancer, bevacizumab has been evaluated in a Phase 2, single-arm trial by the Gynecologic Oncology Group (GOG).22 In 62 evaluable patients, the 6-month PFS was 40.3% and overall objective response rate was 21% with two patients experiencing a complete response. The median duration of response was 10 months. Forty-one patients (66.1%) had received two prior regimens and 26 patients (41.9%) were considered platinum resistant. In another single-arm trial of single-agent bevacizumab in patients with platinum-resistant ovarian cancer who had progressed after either topotecan or liposomal doxorubicin, or both, the objective response rate was 16% in 44 treated patients. [13]
	Among other studies evaluating bevacizumab in advanced ovary cancer, results were recently reported on a Phase 3 randomized trial (GOG-0218) which studied the addition of bevacizumab to first line carboplatin and paclitaxel and continuing bevacizumab monotherapy as maintenance for one year. Patients who received bevacizumab with chemotherapy and as maintenance had a statistically significant progression-free survival advantage. [14]
	In OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy With or Without Bevacizumab in Patients With Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer, patients with recurrent

Study Rationale (cont.)	platinum-sensitive ovarian cancer subjects were randomly assigned to gemcitabine and carboplatin chemotherapy plus either bevacizumab or placebo for six to 10 cycles. Bevacizumab or placebo, respectively, was then continued until disease progression. The primary end point was progression-free survival (PFS) by RECIST; secondary end points were objective response rate, duration of response (DOR), overall survival, and safety. Overall, 484 patients were randomly assigned. PFS for the bevacizumab arm was superior to that for the placebo arm (hazard ratio [HR], 0.484; 95% CI, 0.388 to 0.605; log-rank P _ .0001); median PFS was 12.4 v 8.4 months, respectively. The objective response rate (78.5% v 57.4%; P _ .0001). This study revealed that gemcitabine and carboplatin chemotherapy plus bevacizumab followed by bevacizumab until progression resulted in a statistically significant improvement in PFS compared with GC plus PL in platinum-sensitive recurrent ovarian cancer. [15] **Endometrial cancer:** Endometrial cancer is the most common gynecologic malignancy and the eighth most common cause of cancer death among American women. While most endometrial cancers are likely to present at an early stage, approximately 25 % of early stage and more than 50 % of advanced stage cancers will recur. Women diagnosed with advanced stage endometrial cancer have a similar outcome to those women with advanced ovarian cancer. Current adjuvant therapies for these patients are not very effective and there are limited options for patients with distant disease. Patients with advanced stage disease at the time of diagnosis have a high risk for recurrence. The median survival after recurrence is ten months and the five-year overall survival for patients who have recurred is less than 15%. Unfortunately, recurrent disease is generally not curable, and response rates for cytotoxic chemotherapy are in the 15-20 % range. Therefore efforts in finding effective treatments for this population need to be pursued. New biologic or targeted therapies based on an understanding of the underlying tumor biology hold promise for better outcomes for women with advanced or recurrent endometrial cancer. Activating mutations in fibroblast growth factor receptor 2 (*FGFR2*) in endometrial tumors is a promising new approach for the development of targeted therapeutic agents. Preclinical studies have demonstrated that mutant FGFR2 endometrial cell lines are highly sensitive to FGFR tyrosine kinase inhibitors. AL3818 (anlotinib hydrochloride) is a novel small molecule dual receptor tyrosine kinase inhibitor, which shows highly selective inhibition of fibroblast growth factor receptor (FGFr) and vascular endothelial growth factor receptor (VEGFR). Preclinical studies of this agent in mouse models, including various cancer xenografts, have demonstrated that treatment of the mice with AL3818 will induce reduction in tumors of tumor bearing mice. The majority of the mutations identified are identical to germline mutations in *FGFR2* and *FGFR3* that result in both ligand-independent and ligand-dependent receptor activation. Mutations that predominantly occur in the subtype of endometrial cancer, are mutually exclusive with *KRAS* mutation, but occur in the presence of *PTEN* abrogation. Preclinical studies have demonstrated that mutant FGFR2 endometrial cell lines are highly sensitive to FGFR tyrosine kinase inhibitors. There is evidence that angiogenesis plays a role in endometrial cancer disease progression and prognosis. [16, 17, 18, 19]

Study Rationale (cont.)	A Phase II GOG study of thalidomide in refractory endometrial cancer demonstrated an association between elevated plasma VEGF levels and poor prognosis. [20] VEGFR was found to be present in up to 2/3 of endometrial adenocarcinoma specimens, [21] and VEGF expression was higher in endometrial adenocarcinoma than in normally cycling endometrium. [22, 23, 24] VEGFR-2(flk-1) and VEGFR-3 were found to be poor prognostic factors in endometrial cancer.

VEGF-A/VEGF-1 expression is associated with decreased 5 and 10-year disease-free survival in post-menopausal patients with endometrial carcinoma. [25] Further study of the VEGF, VEGF-R (KDR) pathway in stage I endometrial carcinoma demonstrated a worse prognosis for tumors bearing activated KDR (pKDR). [26] This study identified pKDR in endometrial cancer, endothelial and stromal cells. pKDR levels correlated with KDR/VEGF complex levels. KDR activation was also associated with an elevation with HIF-1alpha, an up-regulator of VEGF. These relationships point to a VEGF autocrine loop which can serve as a therapeutic target.

Single agent bevacizumab has been studied by the GOG in study GOG-0229E. [27] Eligible patients had persistent or recurrent endometrial carcinoma after receiving 1-2 prior cytotoxic regimens, measurable disease, and GOG performance status < 2. Treatment consisted of bevacizumab 15 mg/kg IV q 3 weeks until disease progression or prohibitive toxicity. Primary endpoints were progression-free survival (PFS) at 6 months, objective response rate, and toxicity by NCI CTCAE v3.0. The clinical trial was carried out in a flexible 2-stage group sequential design intended to detect either cytostatic or cytotoxic activity. Median age was 62 (range 44-84) years, and prior treatment consisted of 1 or 2 regimens in 33 and 20 patients, respectively. Twenty-eight patients (52.8%) had prior radiation. Response rate was 13% and 6 month PFS was 40%.

Cervical Cancer:

Currently there are around 530,000 new cases of cervical cancer diagnosed worldwide with 280,000 deaths occurring each year. Last year (2013) 12,340 new cases were diagnosed and 4,030 patients died in the US alone. Eighty percent of incident cervical cancer cases and deaths occur in developing countries because of socioeconomic challenges, pattern of health care delivery, and societal factors. Cervical cancer is diagnosed at advanced stages in > 80 % of women in developing countries. More than 80 % of affected women are diagnosed in advance stages and are usually young, working, and raising children, which creates substantial social problems.

Prognostic factors include clinical stage at time of diagnosis, tumor size, lymphovascular invasion, and parametrial and lymph node involvement. Early stages (stage IA to IB2) are often treated surgically and later stages require multidisciplinary treatments with either concurrent chemoradiation (the predominant treatment in the United States) or neoadjuvant chemotherapy followed by surgery. Central recurrences can be cured with directed pelvic exenteration, but distant recurrences remain uniformly fatal.

There is accumulating evidence that angiogenesis plays a central role in cervical carcinogenesis and disease progression. For example, using IHC, Dobbs and colleagues recently demonstrated a direct association of both microvessel density (MVD) and VEGF expression with increasing levels of cervical neoplasia in cone biopsy and hysterectomy specimens. [28] The same relationship was identified in lesions studied by Dellas and associates using IHC for CD-31.64 Using similar methodology, Tokumo and associates recently showed that the expression of VEGF was highly correlated with MVD in the

| Study Rationale (cont.) | primary invasive carcinomas from 73 patients treated with radical hysterectomy. Interestingly, this group found that VEGF expression was significantly greater in adenocarcinomas than in squamous cell tumors. [29]

The impact of angiogenic activity on clinical outcome in patients with cervical cancer has yet to be convincingly determined. However, several historical cohort studies have suggested a negative prognostic relationship. For example, Obermair and colleagues in Vienna recently reported that in a population of 166 women with stage IB cervical carcinoma treated with radical surgery, the estimated five-year survival for patients whose tumors had an MVD of less than or equal to 20 per high power field was 90% compared with 63% for those with an MVD of greater than 20. [30] Importantly, multivariate analysis showed this association to be independent of lymph node status, tumor size, and the use of adjuvant radiotherapy. Dellas and colleagues studied CD-31 expression and demonstrated the same prognostic association by quantitative IHC in 58 patients with stage IB cervical carcinoma. Using stepwise regression analysis, they found that CD-31 expression was an independent prognostic indicator for overall survival, independent of depth of stromal invasion and lymph node status. A more recent study in the British literature using similar methodology and patients confirms these results. [31, 32] Similar conclusions have been reached in patients with locally advanced disease treated with radiotherapy. In a study of 111 women, tumor angiogenesis, as measured by MVD, was associated with poor loco-regional control and overall survival, and MVD was a significant prognostic factor within a Cox multivariate analysis. [33]

Angiogenesis in cervical neoplasia: microvessel quantitation in precancerous lesions and invasive carcinomas with clinicopathological correlations. Gynecol Oncol 1997;67:27-33)Similar conclusions have been reached in patients with locally advanced disease treated with radiotherapy. In a study of 111 women, tumor angiogenesis, as measured by MVD, was associated with poor loco-regional control and overall survival, and MVD was a significant prognostic factor within a Cox multivariate analysis. [34]

Given the activity of bevacizumab in non-small cell lung cancer and the potential shared tumor biology between NSCLC and cervical cancer, a phase II evaluation of bevacizumab at 15 mg/kg q21 days was undertaken within the GOG (protocol 227C). [35] Among the 46 eligible and evaluable patients, 38 (82.6%) had received prior pelvic radiation as well as either one (n=34, 73.9%) or two (n=12, 26.1%) cytotoxic regimens for recurrent disease. Notable grade 3/4 adverse effects at least possibly related to bevacizumab included: neutropenia (n=1), anemia (n=2), gastrointestinal (n=4), hypertension (n=7), thrombo-embolism (n=5), other cardiovascular (n=2), vaginal bleeding (n=1), and fistula (n=1). One grade 5 infection was observed. Five patients (10.9%, 2-sided 90% C.I. 4% to 22%) experienced partial responses, and 11 patients (23.9%, 2-sided 90% C.I. 14% to 37%) survived progression-free for at least 6 months. The median response duration was 6.21 months (range, 2.83-8.28 months). The median PFS and OS for all patients were 3.4 months (95% C.I. 2.53, 4.53) and 7.29 months (95% C.I. 11, 10.41), respectively. These results suggest that bevacizumab is well-tolerated and active in the second- and third-line treatment of patients with recurrent cervical cancer and performs favorably when compared to historical phase II GOG trials in this setting.

A Randomized Phase III Trial of Cisplatin Plus Paclitaxel With and Without NCI-Supplied Bevacizumab vs. the Non-Platinum Doublet, Topotecan Plus Paclitaxel, With and Without NCI-Supplied Bevacizumab, in Stage IVB, Recurrent or Persistent Carcinoma of the Cervix |

Study Rationale (cont.)	(GOG240) recently resulted and led to FDA approval of bevacizumab in advanced cervix carcinoma when results revealed that median survival was 17 months with chemotherapy plus bevacizumab and 13.3 months with chemotherapy alone. The response rates were 48% in the chemotherapy plus bevacizumab and 36% in the chemotherapy only arm (p=0.0078). [36] ************* Thus, exploring the utility of a multi-kinase inhibitor with anti-angiogenic activity is reasonable in advanced or recurrent ovarian cancer, endometrial and cervical carcinomas. AL3818 (anlotinib hydrochloride) is a novel small molecule dual receptor tyrosine kinase inhibitor, which shows highly selective inhibition of fibroblast growth factor receptor (FGFr) and vascular endothelial growth factor receptor (VEGFR). Preclinical studies of this agent in mouse models, including various cancer xenografts, have demonstrated that treatment of the mice with AL3818 will induce reduction in tumors of tumor bearing mice. AL3818, discovered by Advenchen Laboratories, LLC in US and developed by Jiangsu Chia Tai Tianqing Pharmaceutical Company Ltd. (CTTQ)in China, was modeled after other multi-targeted anti-cancer drugs, such as sorafenib, but has been modified based on its molecular structure to improve the pharmacodynamic properties as well as physical and chemical properties and characteristics. AL3818 is currently being evaluated as an anti-tumor product in patients with solid tumors as a once daily oral immediate release capsule. The dose for the proposed phase 1b/2a trial is based on animal GLP toxicology data and clinical experience gained with a completed Phase 1 dose escalation trial (in China) where dose escalation to 16 mg/day was achieved without significant side effects with a dosing regimen of 2 weeks treatment and 1 week rest.

Study Design	This protocol will be divided into two parts: Part 1 will evaluate the safety and tolerability of adding oral AL3818 to standard platinum-based chemotherapy with carboplatin and paclitaxel; Part 2 will evaluate the safety and preliminary efficacy of AL3818 when given concurrently with chemotherapy at the MTD from Part 1 of this study and as maintenance therapy for up to 18 months. All subjects in Part 1 and Part 2 of this study will be permitted to continue therapy with only safety monitoring and bimonthly assessments for progression, if AL3818 is well tolerated and the subject has stable disease or better.

Up to 54 subjects will be enrolled in this clinical trial.

Part 1 will include a sequential evaluation of 3 subjects per cohort up to 3 subjects in total. Cohort 1 will initiate at a dose of 12 mg of AL3818 (administered on Day 8 of each cycle for a 7 days off and 14 days on AL3818 schedule) combined with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) plus paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle), for six cycles of 21 days. After three subjects have completed one cycles of therapy without a DLT then Part 2 may begin.

Each subject in Part 1 will subsequently be allowed to continue five additional 21-day cycles through Day 126 (See Appendix A1). If the subject is tolerating AL3818 well and at least stable disease by radiographic assessments, they may continue on treatment as described in Appendix A3.

Subjects will then be assessed for disease progression after each six complete 21-day cycles of therapy (Day 127) in Part 1. Patients may continue on therapy for additional 21-Day cycles if the therapy is well tolerated. Efficacy assessments and disease progression (RECIST imaging) will be assessed every three 21-Day cycles. If study medication is discontinued for any reason the subjects will be assessed for safety for at least 21-Days after the last dose of AL3818.

For Part 1 of this study, a Dose Limiting Toxicity (DLT) event is defined as any of the following events that are assessed by the Investigator as probably or possibly related to AL3818 and occur during or after the initial dosing period of Day 8 through Day 21 of cycle one of therapy.
1. CTCAE Grade 4 event
2. Grade 3 thrombocytopenia with bleeding
3. Grade 3 non-hematologic toxicity, including Grate 3 nausea, vomiting, diarrhea and hypertension that continues more than 72 hours despite optimal medical management (Note: The prophylactic use of antihypertensive agents for Grade 1and Grade 2 hypertension in order to minimize the occurrence of more severe or persistent hypertension while undergoing treatment with AL3818 does not constitute a Grade 3 toxicity)
4. Grade 3 ALT or AST lasting > 7 days, based on Hy's Law criteria
5. Grade 3 febrile neutropenia (< 1,000 neutrophils/mm^3)
6. Grade 3 hematologic toxicity with duration > 7 days

If a DLT is experienced in any cohort, the cohort will be expanded to 6 subjects and the dose of AL3818 will be lowered to 10 mg. If at 10 mg a DLT is experienced, the dose of AL3818 will be lowered to 8 mg and so on for each DLT experienced. If two (2) DLTs are experienced in any cohort, the study will be paused until the safety events are evaluated. The maximum tolerated dose (MTD) will be defined as the dose level below that where 2 DLTs are experienced.

| Study Design (cont.) | Part 2 of this study will include up to 45 additional subjects with metastatic endometrial cancer (approx. 15), ovarian cancer refractory to platinum therapy (approx. 15) or cervical cancer refractory to standard therapy (approx. 15). Each subject will receive a dose of up to 12 mg AL3818 (administered on Day 8 of each cycle for a 7 days off and 14 days on AL3818 schedule) or a maximum of the MTD from Part 1 of this study combined with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) and paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle) for six continuous 21-Day cycles of therapy and continued as maintenance therapy for up to 18 months. For cervical cancer, cisplatin (recommended dose of 75 mg/m^2 would be preferred over carboplatin. If a subject experiences an intolerable side effect, a dose reduction or a dose interruption is allowed at the discretion of the investigator as described in Section 3.4.4 and 3.4.5. Subjects will be evaluated by RECIST (version 1.1) response at the end of each three cycles of therapy in Part 2 of the study. Safety reporting will be continued for 21-Days from the last dose of study medication if discontinued for any reason. During Part 2 any subject experiencing an adverse event that is consistent with the DLT criteria above will be considered an SAE and reported to the Medical Monitor who will assess the case. If two similar events are reported, new enrollment in the study will be stopped until the medical monitor can evaluate safety. All subjects in Part 1 and 2 of this trial will be eligible to continue therapy provided they have a least stable disease or better and are, in the opinion of the investigator, adequately tolerating treatment with AL3818. |
| Sample Size | Up to 48 subjects (Possibly up to 54) |

Main Inclusion Criteria	1. Female subjects 18 years of age or older
	2. Subjects may be enrolled with previous histologically proven diagnosis of the following:

        a. Endometrial Cancer: Patients must have recurrent or persistent endometrial carcinoma, which is refractory to curative therapy or established treatments. Histologic diagnosis will be reviewed by the treating institution.

            Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified, mucinous adenocarcinoma, squamous cell carcinoma, and transitional cell carcinoma.

            Initial treatment may have included chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy; antiangiogenic therapy (e.g. bevacizumab) as part of adjuvant therapy is allowed. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer was counted as a systemic chemotherapy regimen. Patients are not allowed to have received additional cytotoxic or non-cytotoxic therapy for management of recurrent or persistent disease. Endometrial patients must be chemotherapy naïve or could have had adjuvant radiation therapy.

        b. Ovarian cancer: Patients must have recurrent or persistent ovarian or primary peritoneal cancer, which is refractory to established treatments.

            Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified.

            Patients must have received one prior platinum-based chemotherapeutic regimen for the management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial therapy may have included high-dose therapy, consolidation, or extended therapy adminitstered after surgical or non-surgical assessment. Antiangiogenic therapy (e.g. bevacizumab) as part of adjuvant therapy is allowed.

            Patients must have had disease progression $\geq$ 6 months after completion of front-line platinum-based chemotherapy..

            Patients are not allowed to have received additional cytotoxic or non-cytotoxic therapy for management of recurrent or persistent disease.

        c. Cervix cancer: Subjects diagnosed with histologically confirmed squamous cell carcinoma of the cervix, which are resistant to conventional platinum therapy and have relapsed within $\geq$ 6 months of treatment. Patients with the following histologic epithelial cell types are eligible: squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma.

    requiring treatment, after one prior line of therapy, with further platinum-based chemotherapy $\geq$ 6 months after their last cycle of first-line chemotherapy and 6 weeks after maintenance that is not chemotherapy based.

Main Inclusion Criteria (cont.)	Patients must have received one prior platinum-based chemotherapeutic regimen for the management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial therapy may have included high-dose therapy, consolidation, or extended therapy administered after surgical or non-surgical assessment. Antiangiogenic therapy (e.g. bevacizumab) as part of adjuvant therapy is allowed.

3. All patients must have measurable disease. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be $\geq$ 20mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or $\geq$ 10mm when measured by spiral CT.

4. Life expectancy $\geq$ 3 months

5. Subject must be suitable for oral administration of study medication

6. Patients must have signed an approved informed consent and authorization permitting release of personal health information.

7. Patient must have adequate:
    a. Bone Marrow Function: Absolute neutrophil count (ANC) greater tgen of equal to 1,500/mm3, equivalent to Common Toxicity Criteria (CTC) grade 1. Platelets greater than or equal to 100,000/mm3
    b. Renal Fucntion:: Creatinine less than or equal to 1.5 x institutional upper limit normal (ULN), CTC grade 1. Note: If creatinine is greater than 1.5 x ULN, creatinine clearance must be greater than >50 mL/min.
    c. Hepatic Fucntion: Bilirubin less than or equal to 1.5 x ULN (CTC grade 1) or less than or equal to 3.0 x ULN for subjects with Gilbert Syndrome; AST and ALT less than or equal to 3.0 ×ULN.
    d. Coagulation profile: PT such that international normalized ratio (INR) is $\leq$ 1.55 (or an in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin or low molecular weight heparin) and a PTT < 1.2 times control.

8. ECOG performance status $\leq$ 2

9. Subjects of child-bearing potential must agree to use contraceptive measures starting 1 week before the administration of the first dose of AL3818 until 4 weeks after discontinuing study drug

10. Subjects of child-bearing potential must have a negative serum pregnancy test prior to study entry and cannot be lactating.

11. Ability and willingness to comply with the study protocol for the duration of the study and with follow-up procedures

Main Exclusion Criteria	1. Subjects who have received prior treatment with an FGFr inhibitor or antagonist of FGFr. Prior anti-VEGF or anti-angiogenic therapy is allowed.
	2. Patients who have received prior antiangiogenic therapy, including bevacizumab, sorafenib, sunitinib.
	3. Patients with serious, non-healing wound, ulcer or bone fracture.
	4. Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.
	5. Patient with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases or history of cerebrovascular accident (CVA, stroke) transient ischemic attack (TIA) or subarachnoid hemorrhage within 6 months of the first date of treatment on this study.
	6. However, patients with metastatic CNS tumors may participate in this trial, if the patient is > 4 weeks from therapy completion (including radiation and/or surgery), is clinically stable at the time of study entry and is not receiving corticosteroid therapy.
	7. Patients with proteinuria. Patients discovered to have a urine protein of 1+ on dipstick or $\geqslant$ 30 mg/dl at baseline should undergo a 24-hour urine collection, which must be an adequate collection and must demonstrate < 1000 mg protein/24 hr to allow participation in the study.
	8. Patients with clinically significant cardiovascular disease; this includes: Uncontrolled hypertension; Myocardial infarction or unstable angina within 6 months prior to registration; New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix F); Serious cardiac arrhythmia requiring medication; Grade II or greater peripheral vascular disease (Appendix F)
	9. Patients who are pregnant or nursing. To date, no fetal studies of AL3818 in animals or humans have been performed. Therefore, AL3818 should not be administered to pregnant women. Subjects will be apprised of the large potential risk to a developing fetus. It is not known whether AL3818 is excreted in human milk. AL3818 should not be administered to nursing women. Women of childbearing potential must agree to use contraceptive measures during study therapy and for at least 3 months after completion of AL3818 therapy. Because many drugs are excreted in human milk,
	10. Patients with uncontrolled hypokalemia, hypomagnesaemia, and/or hypocalcaemia.
	11. Hemoptysis within 3 months prior to first scheduled dose of AL3818.
	12. Patients with acute or chronic liver disease, active hepatitis A or B with known cirrhosis or liver dysfunction.
	13. Cytotoxic chemotherapy, immunotherapy, or radiotherapy within 4 weeks (6 weeks in cases of mitomycin C, nitrosourea, lomustine) prior to first scheduled dose of AL3818 or a major surgical procedure within 28 days or minor surgical procedure performed within 7 days prior to first scheduled dose of AL3818.
	14. Concomitant treatment with strong inhibitors or inducers of CYP3A4, CYP2C9 and CYP2C19 who cannot be switched to other alternative medications.
	15. Known history of human immunodeficiency virus infection (HIV).
	16. Subjects with active bacterial infections (other than uncomplicated urinary tract infection) and/or receiving systemic antibiotics.
	17. Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of other cancer present within the last 5 years or whose previous cancer treatment contraindicates this protocol

Main Exclusion Criteria (cont.)	therapy. 18. History of non-malignant GI bleeding, gastric stress ulcerations, or peptic ulcer disease within the past 3-months that in the opinion of the investigator may place the patient at risk of side effects on an anti-angiogenesis product. 19. History of significant vascular disease (e.g. aortic aneurysm, aortic dissection). 20. Intra-abdominal abscess within the last 3 months. 21. History of uncontrolled hypertension that is not well managed by medication, as documented by 2 baseline evaluations taken one hour apart with systolic blood pressure >160 mm or diastolic blood pressure >90 mm Hg pressure, or that in the opinion of the investigator may place the patient at risk when taking a VEGF inhibitor. 22. Pre-existing uncontrolled hypertension as documented by 2 baseline BP readings taken at least one hour apart, defined as systolic bloodpressure (BP) >160 mm Hg or diastolic BP > 90 mm Hg pressure. 23. QTcF>470 msec on screening ECG. 24. A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome). 25. The use of concomitant medications that prolong the QT/QTc interval. 26. Baseline echocardiogram (within 2 months) with left ventricular ejection fraction (LVEF) < 50%. 27. History of difficulty swallowing, malabsorption, active partial or complete bowel obstruction, or other chronic gastrointestinal disease or condition that may hamper compliance and/or absorption of AL3818. 28. History of pancreatitis and/or renal disease or pancreatitis that includes histologically confirmed glomerulonephritis, biopsy proven tubulointerstitial nephritis, crystal nephropathy, or other renal insufficiencies. 29. Treatment with an investigational agent within the longest time frame of either 5 half-lives or 30 days of initiating study drug. 30. Known recreational substance abuse. 31. Known hypersensitivity to AL3818 or components of the formulation.

Dosage and Administration of Study Drug	In Part 1, Cohort 1 will initiate at a dose of 12 mg of AL3818 (administered on Day 8 of each cycle for a 7 days off and 14 days on AL3818 schedule) combined with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) plus paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle), for six cycles of 21 days. In Part 2 subjects will receive a dose of up to 12 mg of AL3818 (administered on Day 8 of each cycle for a 7 days off and 14 days on AL3818 schedule) or a maximum of the MTD from Part 1 of this study combined with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) and paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle) for six continuous 21- Day cycles of therapy and continued as maintenance therapy for up to 18 months. All doses of AL3818 will be given in the fasted state, preferably approximately 30 minutes prior to breakfast or 2 hours after a meal. If a subject experiences gastrointestinal side effects, they may take the product with a light meal, milk or yogurt. A dose reduction may be allowed in any cohort if the subject does not experience a DLT, but side effects are intolerable at any time during therapy.
Safety Analysis	**Data Safety and Monitoring**: Safety summaries will be prepared by the study Medical Monitor after each cohort in Part 1 and when 50 % of the subjects in Part 2 are enrolled. The safety report will be reviewed by a Data Safety and Monitoring Board (DSMB). In some instances, because of unexpectedly severe toxicity, the Medical Monitor may take an immediate action in communication with the investigator and notify the DSMB chairman of any potential unexpected risks to subjects. The frequency and severity of all toxicities are tabulated from submitted case report forms and summarized for review by the Medical Monitor, and Data Safety and Monitoring Board (DSMB). The initial overall review of toxicity is usually performed after completion of the first stage of accrual, at which point accrual is generally suspended pending formal analysis of response and toxicity. All serious and/or unexpected events are communicated to the Medical Monitor, DSMB Chairman, sponsor, and regulatory agencies as mandated in the protocol. These reports are reviewed by the Medical Monitor within two working days for consideration of investigator notification, amendment, or immediate study suspension. In the event of more than 1 treatment-related death that occurs on-study, or more than 2 identical unexpected treatment-related non-hematologic grade 4 toxicities, centralized registration and accrual will be suspended pending further review. All participating institutions will then receive notification of the toxicities and reason for study suspension. Under these circumstances, accrual cannot be re-activated until the study is reviewed by the DSMB. However, patients currently receiving treatment may continue to receive treatment in accordance protocol guidelines at the discretion of their physicians, unless directed otherwise. **Evaluable for efficacy and toxicity**: Only those patients who are deemed "ineligible" or who receive no therapy will be eliminated from the analysis. All patients who receive any therapy will be evaluated for treatment related toxicity. In Part 1, safety variables to be monitored include adverse events, physical examinations, vital signs (specifically including blood pressure), ECGs, and clinical laboratory evaluations including serum chemistry, hematology (including RBC

Safety Analysis (cont.)	morphology and reticulocyte count), and urinalysis (with detailed sediment analysis and proteinuria). Discontinuation of a subject from this clinical trial will be considered if there is a marked prolongation of the QT/QTc interval during treatment with the study drug, especially if the measurement is obtained from more than one ECG. While increases in QT/QTc to > 500 ms or of > 60 ms over baseline are commonly used as thresholds for potential discontinuation, the exact criteria chosen will depend on the risk-tolerance level considered appropriate for AL3818 and recurrent cancer patients evaluated on a case-by-case basis. The clinical ECG database will be derived from the collection of 12-lead surface ECGs. Equipment used will have been recently serviced and calibrated with Machine calibration records and performance data maintained on file. Patients will either undergo ECG testing on a mobile unit available during their clinic visits or in the ECG unit or with trained study staff during screening/enrollment procedures. Safety data will be collected throughout the study and summarized using descriptive statistics. In Part 2, safety variables to be monitored include adverse events, physical examinations, vital signs (specifically including blood pressure), and clinical laboratory evaluations including serum chemistry, hematology (including RBC morphology and reticulocyte count). Safety data will be collected throughout the study and summarized using descriptive statistics. For Part 2, dosing will continue for six continuous 21-Day cycles of therapy. The subject will self-administer medication at home and return to the clinic on Days 8, 15, 22, 29, 43, 64, 85, 106 and 127 of the six 21-day cycles of therapy for study evaluations. If the patient continues therapy for repeat cycles of treatment, the patient will return to the clinic every cycle (21 days) for safety assessments and every 64days for evaluation of progression. If the patient discontinues therapy at any time, a final study visit will occur by 21±3 days after the last dose of AL3818.
Efficacy Analysis	Tumor imaging studies will be performed using an appropriate imaging technique at baseline (Day -14 to -1), and after every three 21-day cycles of therapy for patients in both Part 1 (Only at baseline) or for Part 2. Determination of response assessed by RECIST v1.1.

Study Schedule and Duration	Phase 1 will follow a 7-day off, 14-day on AL3818 therapy schedule (administered on Day 8 of each cycle, 7 days after chemotherapy is administered on Day 1 of each cycle) in combination with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) and paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle). The number of administered cycles will depend on the tolerability of each dose level and the severity and occurrence of side effects and DLTs. Phase 2 will follow a 7-day off, 14-day on AL3818 therapy schedule (administered on Day 8 of each cycle, 7 days after chemotherapy is administered on Day 1 of each cycle) in combination with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) and paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle) for six continuous 21-Day cycles of therapy. Overall duration of the study will be approximately 24-48 months, depending on the rate of enrollment and number.

1.0   INTRODUCTION

1.1   Background

AL3818 (anlotinib hydrochloride) was discovered by Advenchen Laboratories, LLC, and initially developed by CTTQ Pharmaceutical Co., Ltd. in China, as a multi-target receptor tyrosine kinase inhibitor. It can inhibit vascular endothelial growth factor receptors (VEGFR1, VEGFR2/KDR and VEGFR3), stem cell factor receptor (C-kit), platelet derived growth factor receptor (PDGFRβ) and other kinase activity; inhibit VEGFR2-mediated downstream signal transduction, thereby inhibit tumor angiogenesis. It was later discovered to have high potency, mainly on both VEGFr and FGFr, as a dual inhibitor.

AL3818, designed based on computer modeling, inhibits vascular endothelial growth factor receptors (VEGFR1, VEGFR2/KDR and VEGFR3), stem cell factor receptor (C-kit), platelet derived growth factor receptor (PDGFRβ) and other kinase activity. It also inhibits VEGFR2-mediated downstream signal transduction, thereby inhibiting tumor angiogenesis. It was later discovered to have high potency against FGFr (FGFr1, FGFr2 and FGFr3) as well as VEGFr and thus may prove to be a potent dual inhibitor.   The chemical name of AL3818 is 1-[[[4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-Yl]oxy]methyl]cyclopropanaminedihydrochloride, and the common name is anlotinib hydrochloride. The molecular formula is $C_{23}H_{22}FN_3O_3 \cdot 2HCl$ and molecular weight: 480.36.
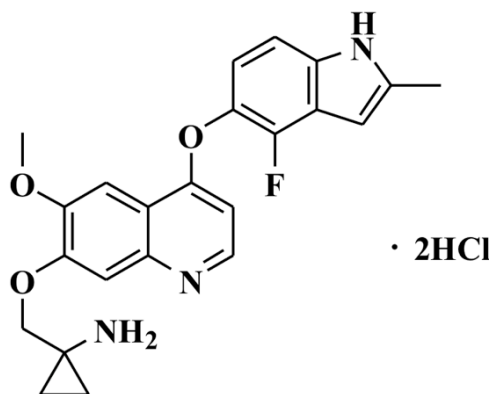
Figure 1.1-1: AL3818 (Anlotinib Hydrochloride)

AL3818 has been shown to have anti-tumor activity both in-vitro and in-vivo. The evaluation of the efficacy of AL3818 in cytotoxicity assays was conducted on 786-O (human renal cancer cell line), A375 (Human melanoma cell line), A549 (adenocarcinomic human alveolar basal epithelial cell), Caki-1 (human clear cell renal cell carcinoma line), U87MG (human primary glioblastoma cell line), MDA-MB-231 (metastatic human breast cancer cell line), HT-29 (human colorectal adenocarcinoma cell line), NCI-H526 (variant small cell lung cancer cell line), HMC-1 (Mastcell leukemia cell line) and many other tumor cell lines in vitro. The results showed that AL3818 had an inhibitory effect on the proliferation of these cell lines in a non-cell type-specific manner. AL3818 significantly inhibited the kinase phosphorylation levels of KDR, and its

activity was similar to Sunitinib, but stronger than Sorafenib. AL3818 also strongly inhibited c-Kit, and PDGFRβ kinase activities at a lower IC50 than Sorafenib.

AL3818 inhibited HUVEC migration, lumen formation and angiogenesis of rat aortic rings, and its inhibitory activity was similar with Sunitinib, but at a lower IC50 compared to Sorafenib. In addition, AL3818 inhibited subcutaneous tumor angiogenesis. The results showed that AL3818 had anti-angiogenic effects.

AL3818 was also compared in in-vivo anti-tumor efficacy models in comparison to Sunitinib and Sorafenib. Anti-cancer activities in various models, including human ovarian cancer (SK- OV-3), human non-small cell lung cancer (Calu-3), human hepatoma (SMMC-7721), human colon carcinoma (SW-620), human renal cancer (Caki-1), and human glioma (U87MG) xenograft models in athymic mice, demonstrated similar activity to Sunitinib in animal models, but was more efficacious than Sorafenib in most models. AL3818 also significantly inhibited colon cancer SW-620, ovarian cancer SK-OV-3, lung cancer Calu-3, hepatoma SMMC-7721 tumor growth and led to some tumor shrinkage; it also had a mild effect on kidney cancer Caki-1 and glioma U87MG.

AL3818 was evaluated with human colon cancer HT-29 and non-small cell lung cancer (NSCLC) A549 xenograph models. Oral administration of AL3818 at 2.5, 8, and 25mg/kg inhibited the growth of human colon cancer HT-29 and NSCLC A549 with improved efficacy compared to Sunitinib but less clinical toxicity. AL3818 also demonstrated significantly better efficacy as compared to Sorafenib in human liver cancer Bel-7402, human breast cancer MDA-MB435 and 786-O human renal cell carcinoma xenograft models in mice. AL3818, with or without dexamethasone, was also more effective than lenalidomide, with or without dexamethasone, in xenografts with NS-1 murine multiple myeloma cells in nude mice.

Thus, AL3818 represents a promising new compound with oral bioavailability and specifically to inhibits vascular endothelial growth factor receptors (VEGFR1, VEGFR2/KDR and VEGFR3), stem cell factor receptor (C-kit), platelet derived growth factor receptor (PDGFRβ) and other kinases. It also inhibits VEGFR2-mediated downstream signal transduction, thereby inhibit tumor angiogenesis. It also has high potency against FGFr as well as VEGFr, and as such acts as a dual inhibitor. The low toxicity observed with AL3818 in animal models with equivalent or superior efficacy as compared to Sorafenib and Sunitinib may provide a unique advantage over current therapies.

The non-clinical testing strategy described below was developed to evaluate the pharmacology, pharmacokinetics and toxicology of AL3818 in accordance with ICH S9 (Guidelines for Nonclinical Evaluation for Anticancer Pharmaceuticals) and applicable FDA guidelines. This nonclinical testing strategy includes:

- Primary Pharmacology of AL3818 was examined in multiple in vitro and in vivo models to evaluate the selective inhibition of the VEGFR1, VEGFR2/KDR, VEGFR3, stem cell factor receptor (C-kit), platelet derived growth factor receptor (PDGFRβ) and other kinases.

- The Secondary Pharmacology of AL3818 was evaluated in formal off-target receptor binding assays that confirm the selectivity of AL3818 towards target receptors as compared to other receptors of concern in the body.

- GLP Safety Pharmacology was performed for cardiovascular function in the dog, respiratory function in the dog and neuropharmacology profile in the mouse.

- The Absorption, Distribution, Metabolism and Elimination (ADME) of AL3818 were evaluated both in vitro and in vivo in various animal and human species used in pharmacology and toxicology testing.

- The plasma protein binding of AL3818 was evaluated in dog, mouse and rat plasma.

- The pharmacokinetics and toxicokinetics of AL3818 was evaluated in mice rats and dogs.

- Single and Multiple-dose toxicology studies were conducted in the mouse, rat and dog up to 13 weeks with GLP studies.

- In vivo impairment of fertility was evaluated in rat.

- In vitro and in vivo genetic and cardiovascular toxicity for AL3818 were assessed.

Nonclinical studies completed for AL3818 demonstrate the selective binding to the target receptors and in vivo efficacy in various tumor bearing animal models. The secondary pharmacology and toxicology studies completed to date also confirm that there are relatively lower side effects in animals at efficacious doses as compared to Sorafenib and Sunitinib.

Full study reports for all referenced studies are available translated from Chinese with the original report provided for reference.

1.2   Nonclinical Assessments

1.2.1   Pharmacology

1.2.2   Anti-Tumor Efficacy and Mechanism of Anlotinib Hydrochloride In Vitro

1.2.2.1   The Effect of Anlotinib Hydrochloride on Receptor Protein Tyrosine Kinase Activity

At the molecular level AL3818 had a very significant inhibitory effect on the activities of vascular endothelial growth factor receptor 2 (VEGFR2/KDR) and VEGFR3. The half inhibitory concentration (IC50) values were 0.2 nM and 0.7 nM, the inhibitory effect on the activities of KDR kinase was 20 times that of the positive control compound Sunitinib and 575 times of the another positive control Sorafenib. The inhibitory effect on the activities of VEGFR3 kinase was 22 times of Sunitinib and 506 times of Sorafenib. AL3818 also had a significantly inhibitory effect on the activities of c-Kit and VEGFR1 kinase. These results indicated that AL3818 was a

multi-targeted tyrosine kinase inhibitor and it had an obvious selectivity to KDR and VEGFR3 kinases. The tyrosine kinase inhibitory activity of AL3818 was stronger than Sorafenib and Sunitinib. AL3818 is also quite potent against FGFr and the inhibition affinity (IC50) against FGFr1, FGFr2 and FGFr3 are at 20 nM, 24 nM and 22 nM respectively.

1.2.2.2   Inhibitory Effect of Anlotinib Hydrochloride On Tumor Cell Proliferation In Vitro

We evaluated and compared the cytotoxicity of AL3818 on 786-O, A375, A549, Caki-1, U87MG, MDA-MB-231, HT-29, NCI-H526, HMC-1 and many other tumor cell lines in vitro. The results showed that AL3818 had an inhibitory effect on the proliferation of these cell lines in a non-cell type-specific manner. The IC50 value was 3.0-12.5µM, which is similar with positive controls (Sorafenib and Sunitinib).

1.2.2.3   The Effect of Anlotinib Hydrochloride On Receptor Tyrosine Kinase And its Mediated Signaling Transduction Pathway

Mo7e (human megakaryoblastic leukemia cell line), U87MG (human primary glioblastoma cell line), HUVEC (Human umbilical vein endothelial cells), A431 (epidermoid carcinoma cell line), BT474 (Invasive Ductal Carcinoma Cell Line) cell lines highly expressed c-Kit, PDGFRβ, KDR, EGFR, HER2 respectively, we studied the effect of AL3818 on receptor tyrosine kinase phosphorylation and its downstream signal transduction pathway with SCF-1, PDGFBB, VEGF, EGF cytokine stimulation. AL3818 significantly inhibited the kinase phosphorylation levels of KDR, and its activity was similar Sunitinib, but more potent than Sorafenib. AL3818 also strongly inhibited c-Kit, and PDGFRβ kinase activities, which was stronger than Sorafenib and weaker than Sunitinib. AL3818 failed to inhibit EGFR and HER2 kinase activities. These results indicated that AL3818, which selectively targeted KDR, was a multi-targeted tyrosine kinase inhibitor.

1.2.2.4   The Inhibitory Effect of Anlotinib Hydrochloride on Angiogenesis

AL3818 inhibited the proliferation of VEGF-stimulated human umbilical vein endothelial cells (HUVEC), which showed stronger inhibitory proliferation than FBS-stimulated HUVEC (Table 3); AL3818 inhibited HUVEC migration, lumen formation and angiogenesis of rat aortic rings, and its inhibitory activity was similar to Sunitinib, but more potent than the positive control Sorafenib. In addition, AL3818 inhibited subcutaneous tumor angiogenesis. The results showed that AL3818 had an anti-angiogenic effect.

1.2.3   Nonclinical Efficacy Models

1.2.3.1   In Vivo Anti-Tumor Efficacy Study of Anlotinib Hydrochloride

To evaluate and compare the anti-tumor activity of AL3818, Sunitinib and Sorafenib on human ovarian cancer (SK-OV-3), human non-small cell lung cancer (Calu-3), human hepatoma (SMMC-7721), human colon carcinoma (SW-620), human renal cancer (Caki-1), and human

glioma (U87MG) xenografted model in athymic mice were utilized. AL3818 significantly inhibited colon cancer SW-620, ovarian cancer SK-OV-3, lung cancer Calu-3, and hepatoma SMMC-7721 tumor growth and led to some tumor shrinkage; it also had a mild effect on kidney cancer Caki-1 and glioma U87MG. The anti-tumor activities of AL3818 were equivalent to sunitinib, but significantly stronger than sorafenib in vivo. AL3818 had a great efficacy both in regular dosing with relatively low dose once a day for 21 consecutive days, as well as with a higher dose once a day for 10 consecutive days (Table 4), suggesting that the flexibility of the clinical regimen. AL3818 treatment did not significantly reduce the weight of mice indicating that AL3818 could be well tolerated in tumor-bearing mice; AL3818 combined with 5-fluorouracil or oxaliplatin, at least in colon carcinoma SW-620 model, did not have mutual synergies, but additive effect of apparent toxicity was not observed.

1.2.3.2 AL3818 Efficacies on Human Colon Cancer HT-29 and Non Small Cell Lung Cancer (NSCLC) A549 Xenograft Models (Study No. 003)

This study was designed to evaluate the efficacy of AL3818 on human colon cancer HT-29 and non-small cell lung cancer (NSCLC) A549 xenograft models. Oral administration of AL3818 at 2.5, 8, and 25 mg/kg can inhibit the growth of human colon cancer HT-29 and NSCLC A549 significantly. AL3818 causes regression of tumor at high and medium doses and has improved efficacy compared to AL3819 (sunitinib). However, AL3818 was also shown greater toxicity compared to AL3819. The data shown to date shows that AL3818 can significantly inhibit the growth of human colon cancer HT-29 and A549 xenograft models by demonstrating greater efficacy than AL3819.

Figure 1.2-1: Oral AL3818, AL3819 Efficacy on Human Colon Cancer HT-29
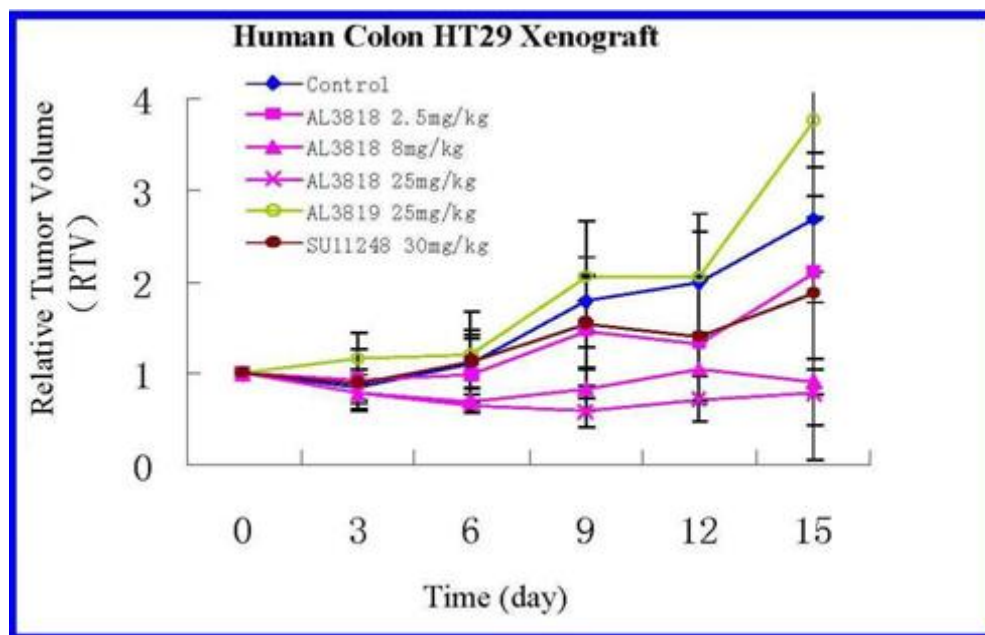
Figure 1.2-2: AL3818, AL3819 Weight Change on HT29
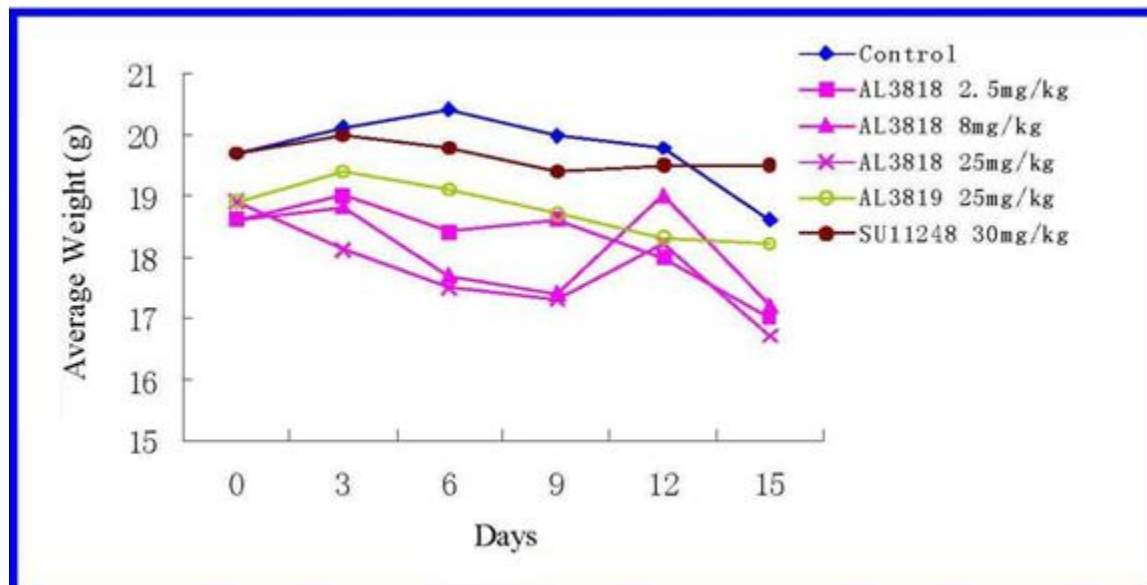
Figure 1.2-3: Oral AL3818, AL3819 Efficacy on Human Colon Cancer HT-29, Tumor Picture
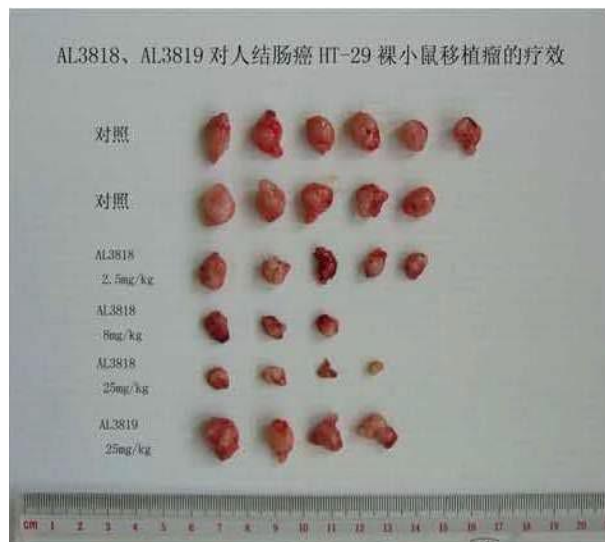
Figure 1.2-4: Oral AL3818, AL3819 Efficacy on Human NSCLC A549
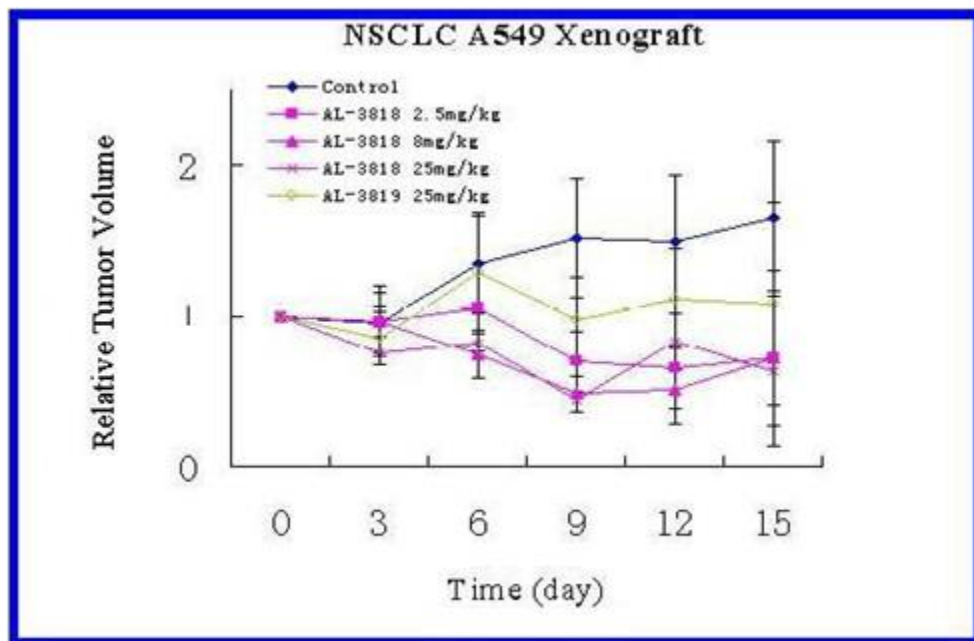
Figure 1.2-5: AL3818, AL3819 Weight Change on A549
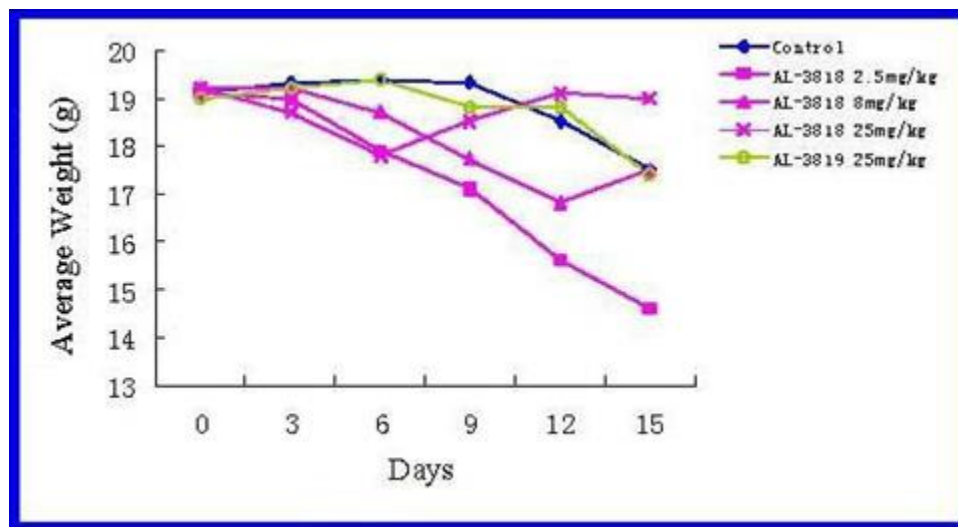
Figure 1.2-6: Oral AL3818, AL3819 Efficacy on Human NSCLC A549, Tumor Picture
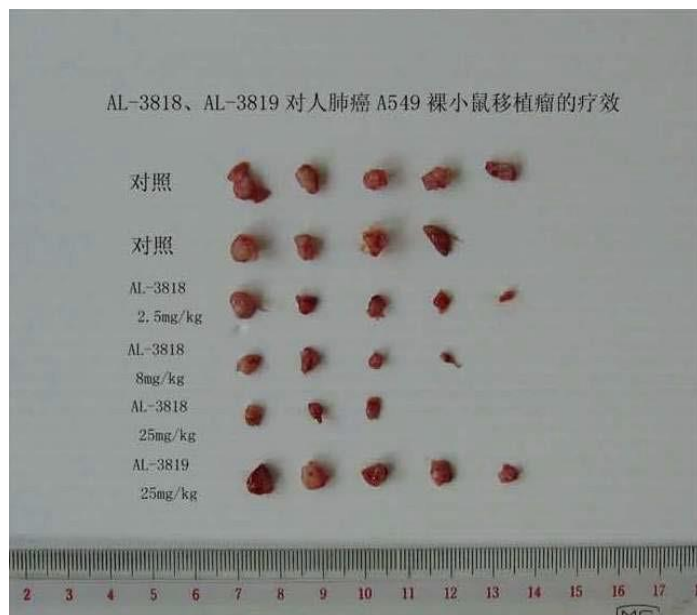
1.2.3.3 AL3818 Compared with Nexavar Efficacy On Human Liver Cancer Bel-7402 Xenograft Model

This study was designed to evaluate the efficacy of AL3818, Nexavar on human liver cancer Bel-7402 xenograft models. AL3818 can inhibit the growth of human liver cancer Bel-7402 dose dependently. Three of 6 mice demonstrated tumor regression at high dose 6 mg/kg with total T/C

of 16.3 %. Nexavar has shown certain inhibition against the Bel-7402 xenograft model at
30 mg/kg with T/C of 65.9 %.

AL3818 was shown to inhibit the growth of human liver cancer Bel-7402 dose dependently.
Three of 6 mice demonstrated tumor regression at high dose 6 mg/kg with total T/C of 16.3 %.
Nexavar has shown certain inhibition against the Bel-7402 xenograft model at 30 mg/kg with
T/C of 65.9 %.

Figure 1.2-7: AL3818 Compared to Nexavar Efficacy on Human Liver Cancer Bel-7402
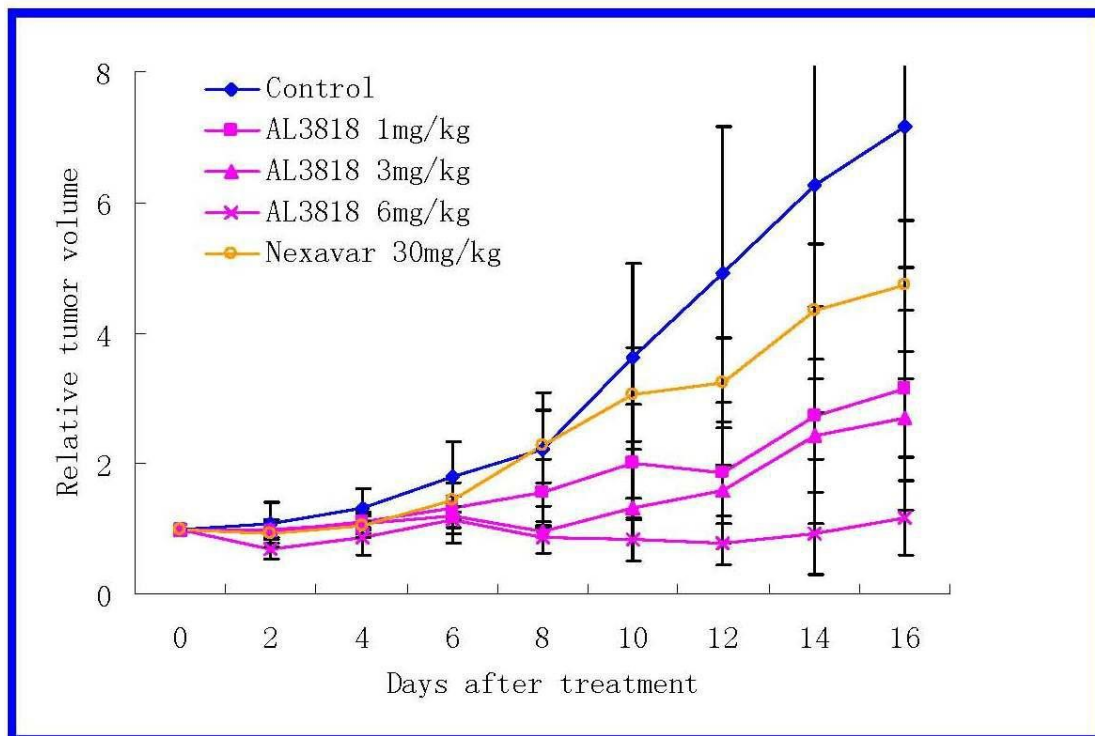
Figure 1.2-8: AL3818, Nexavar Weight Change
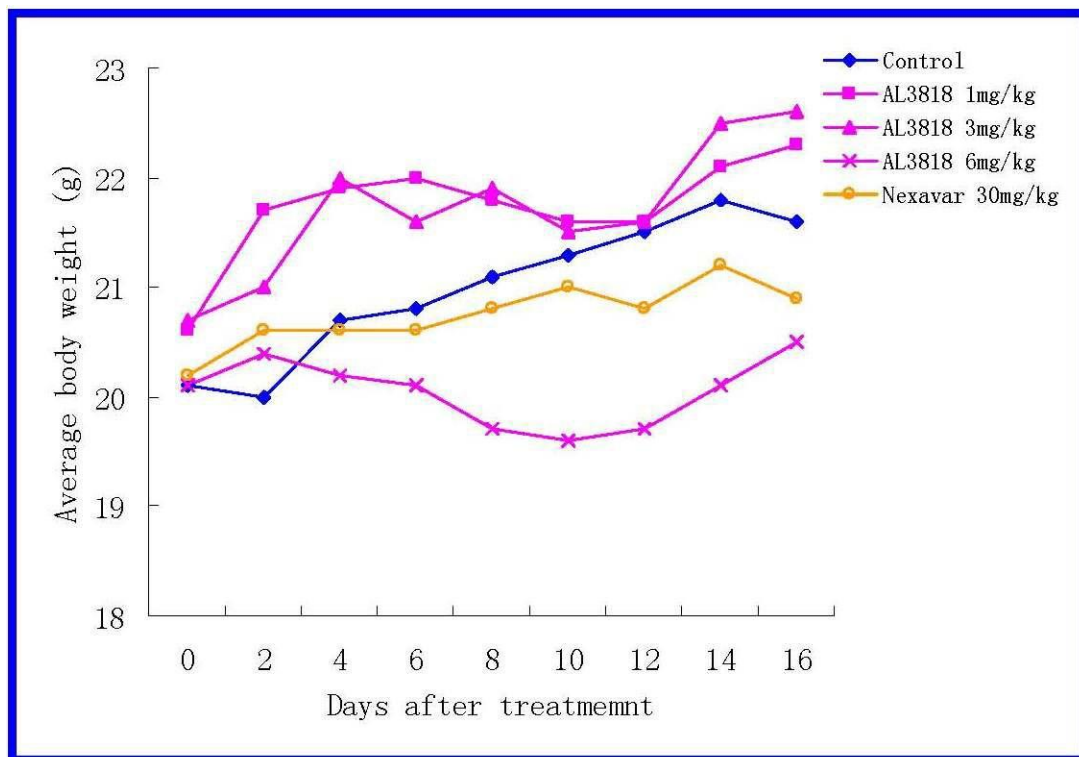
Figure 1.2-9: AL3818, Nexavar Efficacy on Human Liver Cancer Bel-7402, Tumor Picture
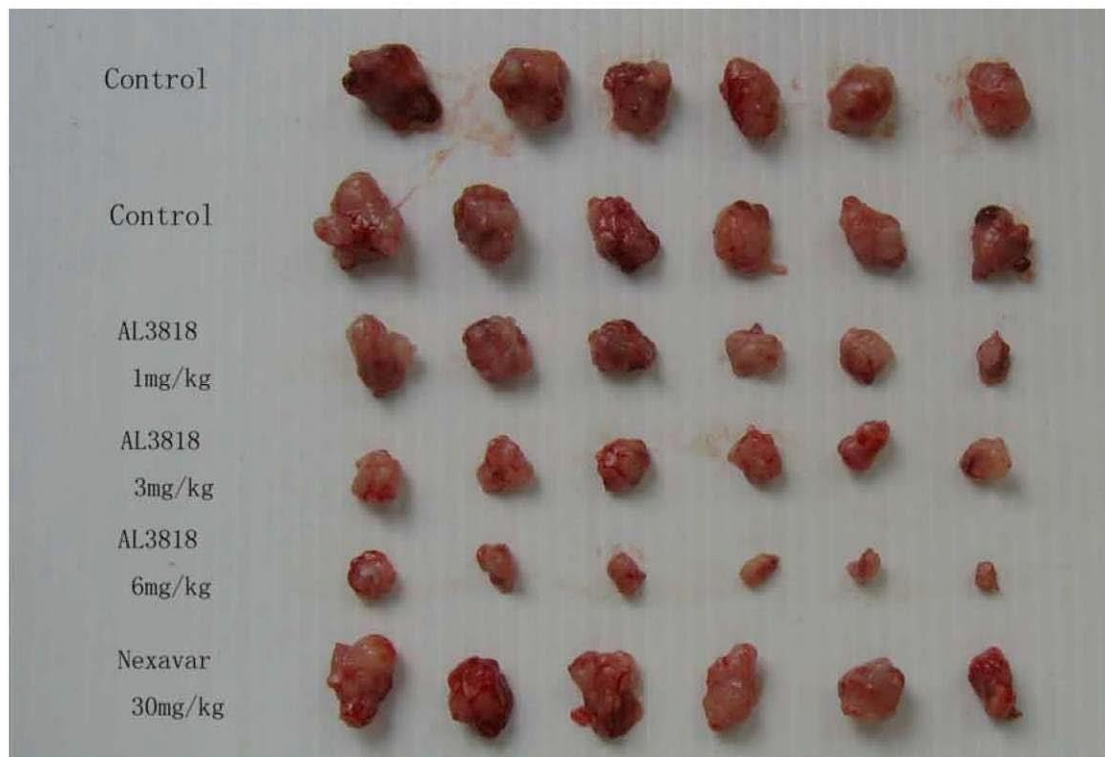
AL3818 has demonstrated significant inhibition of tumor growth in human liver cancer Bel-7402. Nexavar has shown certain inhibition against the Bel-7402 xenograft model without showing strong activity.

1.2.3.4   Effect of AL3818 On Human MDA-MB-435 Breast Cancer Xenograft Model

This study was designed to evaluate and compare the effects of AL3818, AL3808 (sorafenib) and AL3819 (sunitinib) on MDA-MB-435 breast cancer xenograft model in nude mice. The results showed that when administered orally, the tumor inhibitory ratios on human breast cancer MDA-MB-435 cells of AL3818 at 6, 3, 1 mg/kg were 48.32, 38.29 and 32.30 %, respectively. The tumor inhibitory ratios on human breast cancer MDA-MB-435 cells of AL3808 and AL3819 at 30mg/kg were 43.70 and 54.83 %, respectively.

Mice were orally administered with one of the above regimens for consecutive 14 days in a volume of approximately 0.5ml/20 g body weight. From the 13th day following inoculation (D0), the longest diameter a (mm) and the perpendicular shorter diameter b (mm) were measured using *in situ* caliper every 4 days. The calculation formulas of tumor volume (TV) and relative tumor volume (RTV) used were TV = $1/2 \times a \times b2$ and RTV = $Vt/V0$, respectively. V0 and Vt are the tumor volume on D0 and on each measure, respectively. The mice were observed for few more days following the end of dosing and scheduled to be sacrificed on the 31st day (D18). The tumor mass was weighted and the tumor inhibitory ratio (TIR) was calculated.

Mice were treated for 14 consecutive days from the 13th day after inoculation and anatomized on the 31st day. According the RTV, the tumor inhibitory ratios of AL3818 at 6, 3, 1 mg/kg were 48.32, 38.29 and 32.30%, respectively. The tumor inhibitory ratios of AL3808 and AL3819 at 30mg/kg were 43.70 and 54.83 %, respectively.

Figure 1.2-10: Effects of AL3818 on Tumor Volume of Human Breast Cancer MDA-MB-435 in Nude Mice
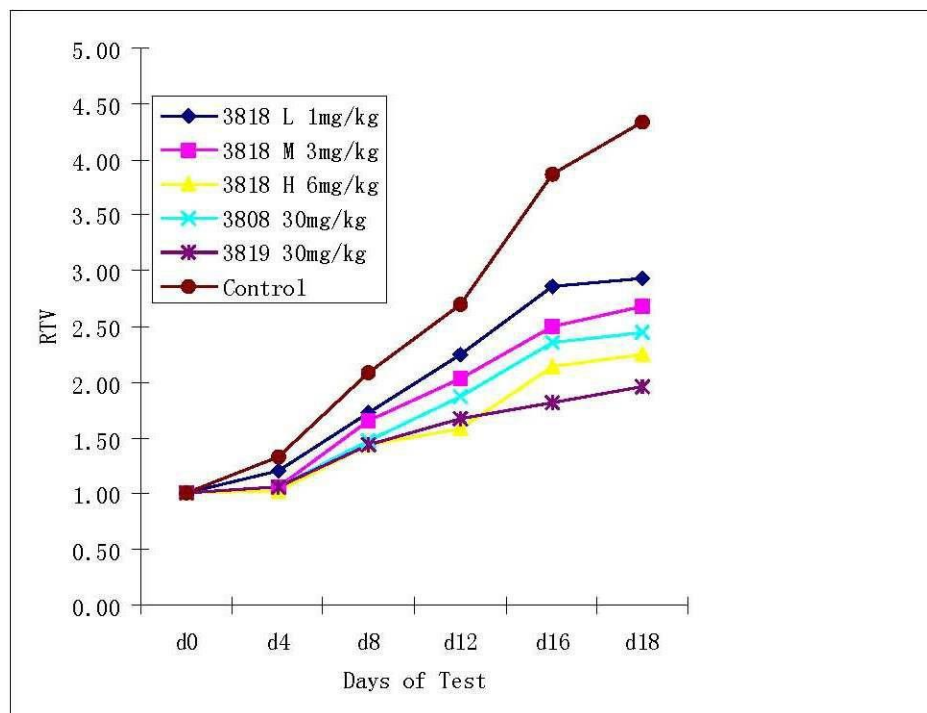
Figure 1.2-11: Effects of AL3818 on the Body Weight of Nude Mice
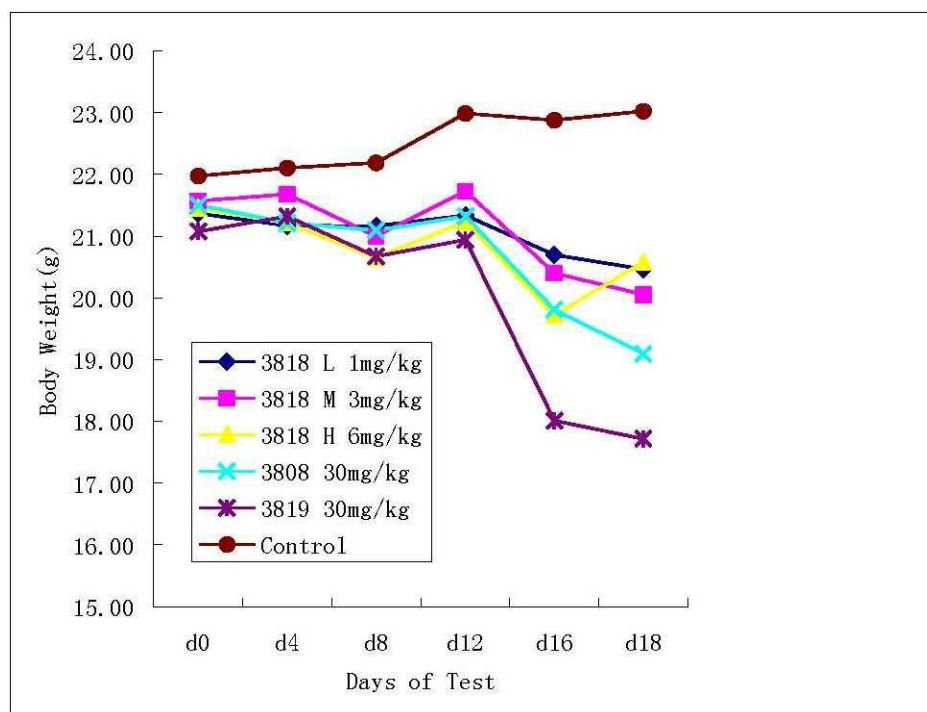
Figure 1.2-12: Growth Inhibition Effects of AL3818 on Human Breast Cancer MDA-MB-435 in Nude Mice
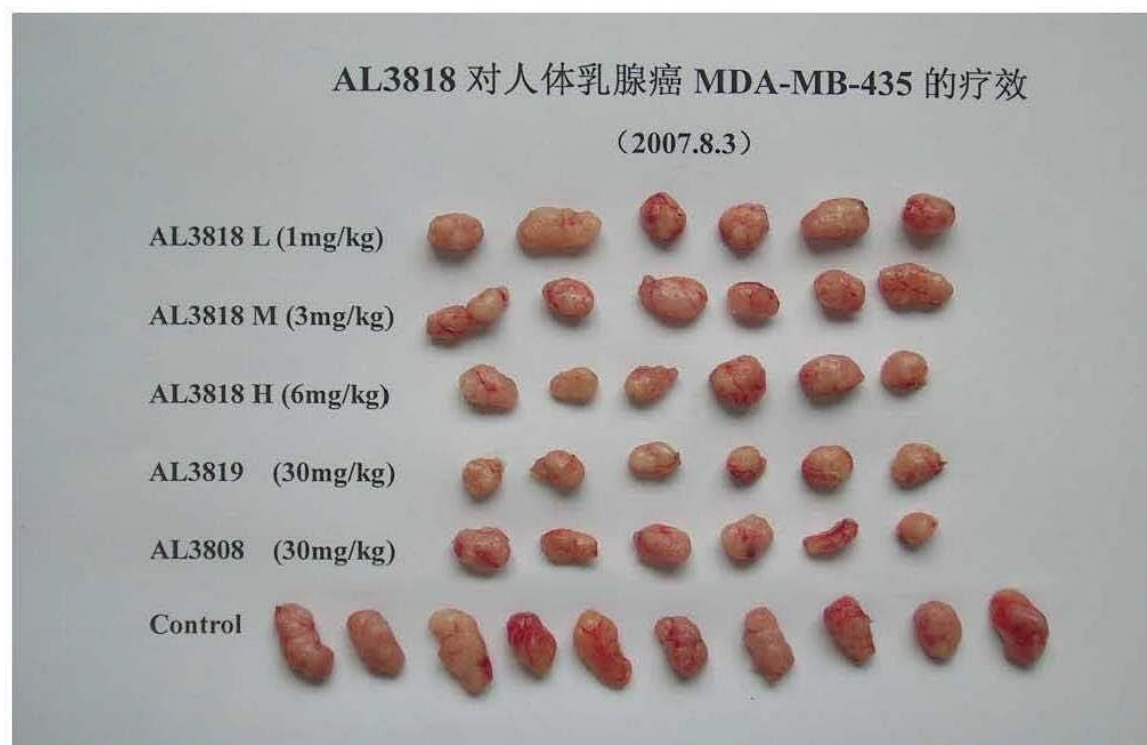
1.2.3.5 Experimental Therapeutic Effect of Al3818 on SMMC-7721, The Human Liver Cancer Xenograft Model

The results showed that when administered orally daily for consecutive 3 weeks, AL3818 inhibited the growth of human liver cancer SMMC-7721 xenograft model in a dose-dependent manner, with the T/C values of 12.3 %, 34.3 and 42.3 % at 9 mg/kg (high dose group, 3 mg/kg (mid dose group) and 1mg/kg (low dose group), respectively. The body weight of nude mice in the high dose group decreased significantly. As a positive control administered orally daily for 3 consecutive weeks, Sorafenib induced a T/C value of 51.5 % at 30 mg/kg without apparent effect on body weight of nude mice.

The well growth of SMMC-7721 tumor tissue was cut into 1.5 mm^3 uniform pieces under sterile conditions. Each nude mouse was inoculated with a piece of the tumor subcutaneously in the right flank using trochar. The tumor was measured by verniercali periodically. When the tumor grew to 120-150 mm^3, mice were randomized to the following groups: AL3818, Sorafenib, or NS as negative control. Mice in each group were administered orally with respective solutions daily for 3 consecutive weeks. The diameter of the tumor and the body weight of the mice were measured twice per week. The longest diameter was recorded as a (mm) and the perpendicular shorter diameter b. The calculation formulas of tumor volume (TV) and relative tumor volume (RTV) used were TV = 1/2×a×b2 and RTV = Vt/V0, respectively. V0 and Vt are the tumor volume on D0 and on each measure. The evaluation index for anticancer activity is relative tumor growth ratio T/C calculated with the formula T/C (%) = (TRTV / CRTV) ×100, in which

TRTV and CRTV are the RTVs of treatment groups and negative group, respectively.
Therapeutic effect evaluation criteria: ineffective if T/C (%) > 60%; effective if T/C (%) < = 60 and p<0.05 by statistical analysis.

Figure 1.2-13: Growth Inhibition Effects of AL3818 on Relative Tumor Volume (RTV) of Human Liver Cancer SMMC-7721 Xenograft
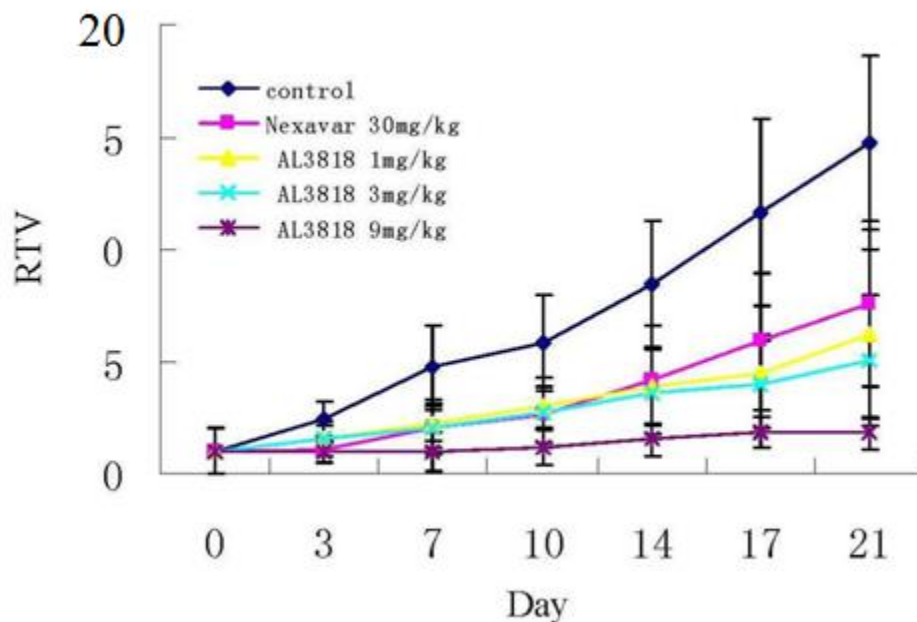
Figure 1.2-14: Growth Inhibition Effects of AL3818 on Tumor Volume of Human Liver Cancer SMMC-7721 Xenograft
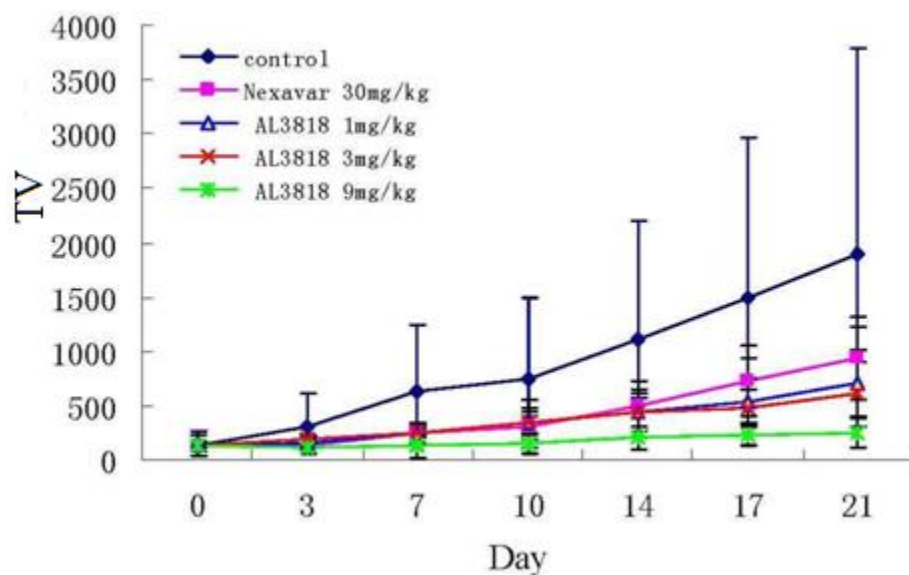
Figure 1.2-15: Effect of AL3818 on the Body Weight of Nude Mice with Human Liver Cancer SMMC-7221 Xenograft
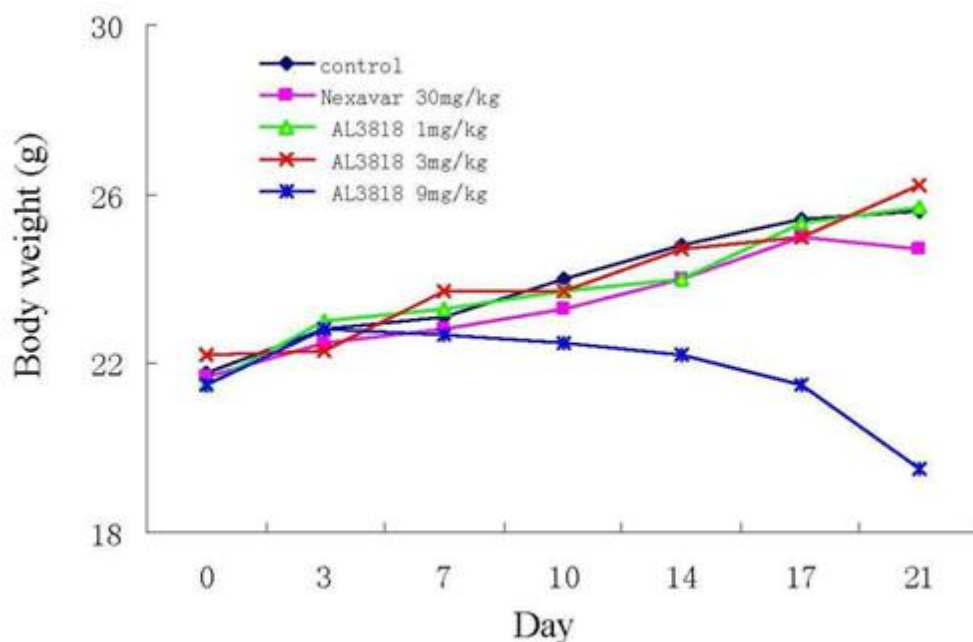
The results showed that when administered orally daily for 3 consecutive weeks, AL3818 inhibited the growth of human liver cancer SMMC-7721 xenograft model in a dose-dependent manner, with the T/C values of 12.3 %, 34.3 % and 42.3 % at 9 mg/kg (high dose group), 3 mg/kg (mid dose group) and 1mg/kg (low dose group), respectively. And the body weight of nude mice in high dose group decreased significantly. As a positive control administered orally daily for 3 consecutive weeks, Sorafenib induced a T/C value of 51.5 % at 30 mg/kg without apparent effect on body weight of nude mice. In conclusion, compared with the positive control Sorafenib, AL3818 more potently inhibited the growth of the human liver cancer SMMC-7721 xenograft in a dose-dependent manner.

1.2.3.6 Effects of AL3818 and AL8327 (Revlimid) Combo-Therapy with Dexamethasone on Murine NS-1 MM Transplanted Tumor in Nude Mice

This study evaluated the anti-tumor activities of AL3818 and AL8327 (Revlimid) combined with dexamethasone on transplanted tumor of NS-1 murine multiple myeloma (MM) in nude mice. Results showed that when AL3818 was administered orally at 3 mg/kg alone and at 1 mg/kg, 3 mg/kg combined with dexamethasone for 12 days, the inhibitory ratios of tumor weight were 48.77 %, 49.85 %, 78.62 %, respectively, and when AL8327 (Revlimid) was administered orally at 50 mg/kg alone and at 15 mg/kg and 50 mg/kg combined with dexamethasone for 12 days, the inhibitory ratios of tumor weight were 18.26 %, 42.34 %, 46.61 %, respectively.

Mice were treated with test compounds for consecutive 12 days from the 10th day after inoculation. They were treated with dexamethasone during the first 4 days and stopped for 4 days then administrated for another 4 days, and sacrificed on the 14th day. The

inhibitory ratios were 23.72 %, 52.01 % for Thalomid at 100 mg/kg alone and ombined
with dexamethasone, respectively. The body weights of nude mice with NS-1
transplanted tumor were declined significantly in combination treatment group of test
compounds and dexamethasone.

Figure 1.2-16: Effect of AL3818(L:1 mg/kg, H:3 mg/kg), AL8327 (Revlimid, L:15 mg/kg, H:50 mg/kg) and Thalomid (H:100 mg/kg) with Dex on Tumor Volume of NS-1 Transplanted Tumor in Nude Mice
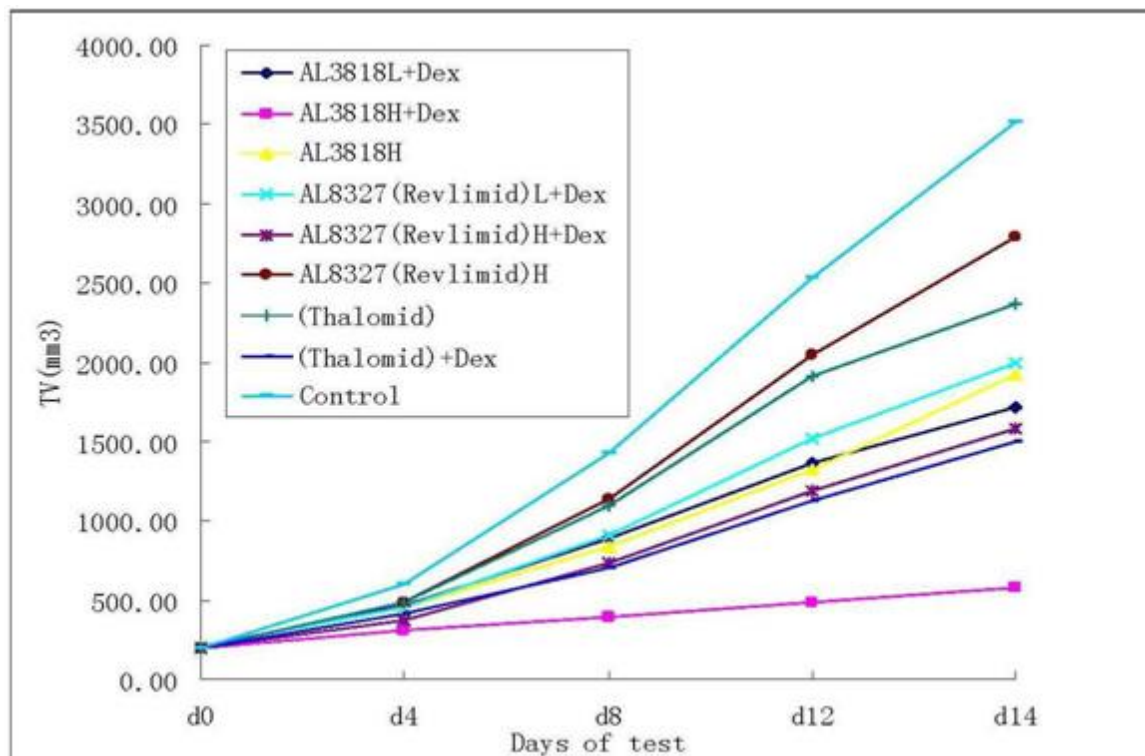
Figure 1.2-17: Effect of AL3818 (L:1 mg/kg, H:3 mg/kg), AL8327 (Revlimid, L:15 mg/kg, H:50 mg/kg) and Thalomid (H:100 mg/kg) with Dex on Relative Tumor Volume of NS-1 Transplanted Tumor in Nude Mice
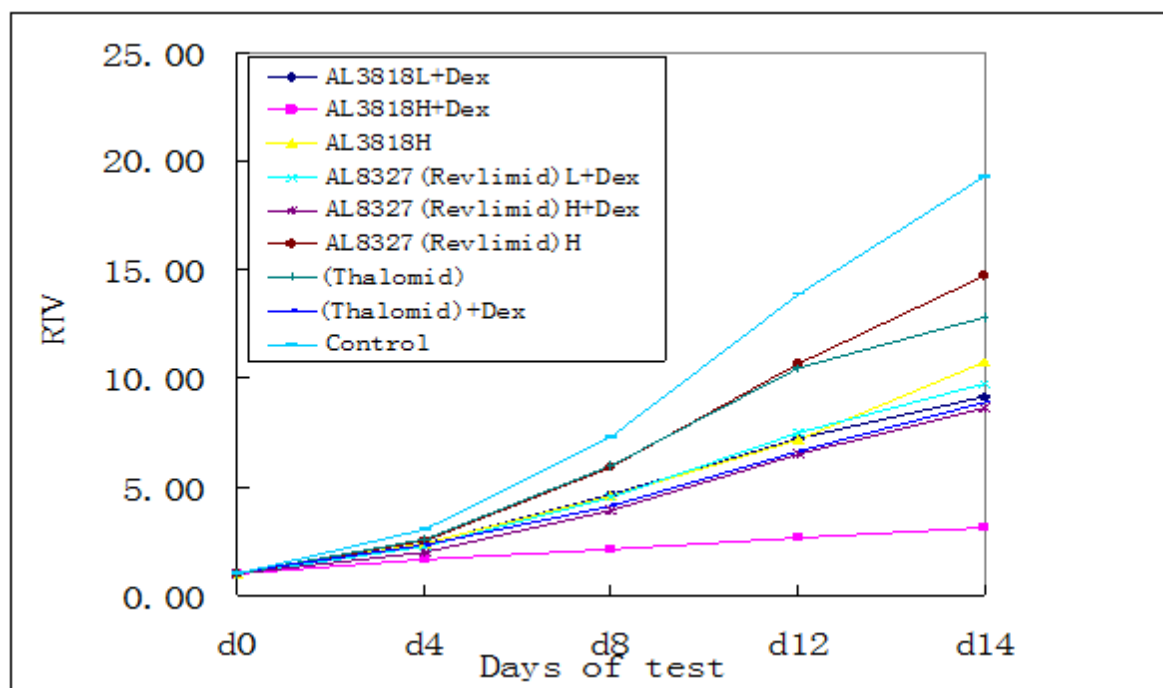
Figure 1.2-18: Effect of AL3818 (L:1 mg/kg, H:3 mg/kg), AL8327 (Revlimid, L:15 mg/kg, H:50 mg/kg) and Thalomid (H:100 mg/kg) Combined with Dex on Body Weight of Nude Mice with NS-1 Transplanted Tumor in Nude Mice
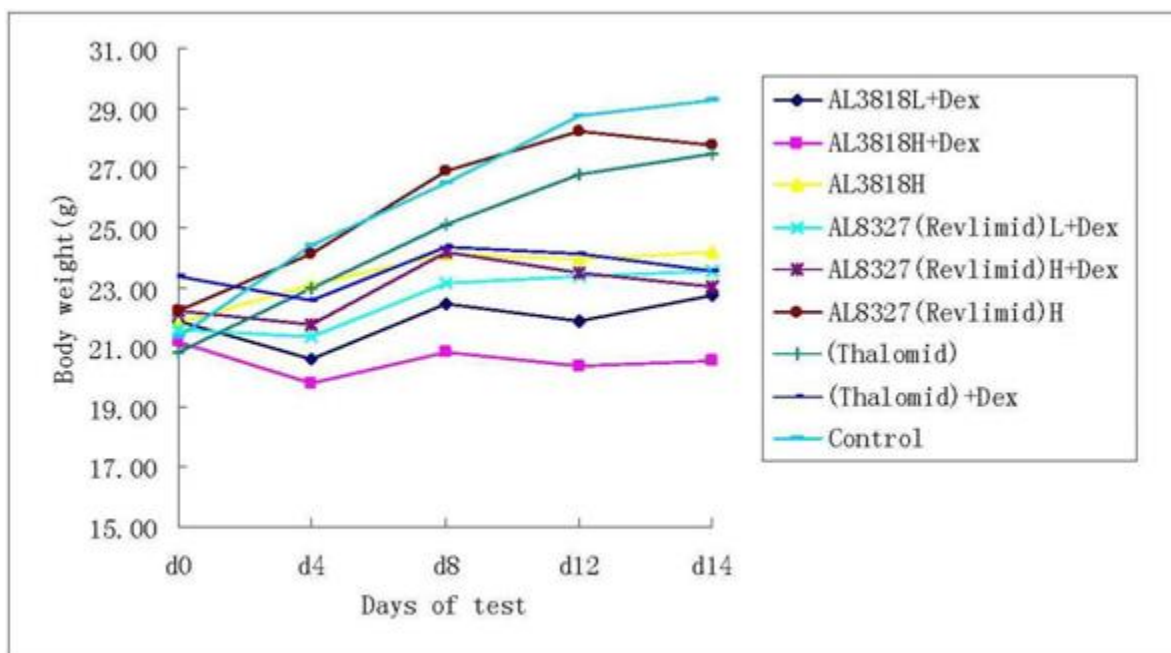
1.2.3.7   Effects of AL3818 and AL8327Revlimid) on Murine NS-1 Transplanted Multiple Myeloma (MM) Tumor in Nude Mice

This study evaluated the anti-tumor activities of AL3818 and AL8327 (Revlimid) on transplanted tumor of NS-1 murine multiple myeloma in nude mice. Results have been shown that when these compounds were administered orally at 3.5mg/kg and 10mg/kg, the inhibitory ratios of tumor weight were 55.50 %, 65.57 % for AL3818 and 11.04 %, 14.19 % for AL8327 (Revlimid), respectively.

Mice were treated for consecutive 10 days from the 11th day after inoculation and sacrificed on the 21stday when compounds were administered orally at 3.5 mg/kg and 10 mg/kg, the inhibitory ratios of tumor weight were 55.50 %, 65.57 % for AL3818 and 11.04 %, 14.19 % for AL8327, respectively, and those of relative tumor volume were 54.74 %, 57.85 % for AL8326 and 3.32 %, 12.18 % for AL8327, respectively. The inhibitory ratios of tumor weight and relative tumor volume were 9.54 % and 12.62 %, respectively for Thalomid at 10 mg/kg.

1.2.3.8   Effect of AL3818 on Human Renal Cell Carcinoma (RCC) 786-O Xenograft in Nude Mice

This study has been shown that when orally administered for consecutive 5 days every week in 4 weeks, AL3818 at 5 mg/kg/day had a significant growth inhibition effect with regression on human renal cell carcinoma (RCC) 786-O xenograft in nude mice, with the tumor volume of this group smaller than that before treatment after 3 days treatment and a T/C on the 28th day of 3.86 %. While AL3818 at 1.5 mg/kg and sorafenib the positive control at 30mg/kg, administered in the same way, did not inhibit the growth of 786-O xenograft significantly, and T/C on the 28th day was 89.29 % and 86.43 %, respectively. All doses of AL3818 and 30mg/kg of sorafenib did not significantly affect the body weight of nude mice in this 786-O xenograft mode.

1.2.4   Toxicology

The toxicology of AL3818 was evaluated in mice, rats and dogs. Both acute and chronic (13-week) GLP toxicology studies were conducted with AL3818.

1.2.4.1   Genotoxicity

A GLP Ames study was conducted to evaluate the in vitro Mammalian Chromosome Aberration Test on mammalian Chinese hamster lung fibroblast (CHL) and mouse bone marrow micronucleus tests were employed to determine the mutagenicity of AL3818. The results of the studies indicated that AL3818 did not cause gene mutation in murine typhoid salmonella. Different concentrations of AL3818 did not induce chromosome aberration in CHL cells with or without S9 metabolic activation. AL3818 not increase the micronucleus rate of bone marrow polychromatic erythrocytes of mice.

1.2.4.2   Single Dose Toxicity Studies

1.2.4.2.1   Acute Oral Toxicity in Mice

A GLP acute toxicity study was conducted in the mice. Single intragastric administration of AL3818 at the dose of 0, 800,1000, 1250, 1563 and 1953 mg/kg was administered. LD50 was 1735.9 mg/kg in 14-day observation period and the 95 % confidence limit was 1365.5 - 5474.6mg/kg. However, LD50 was 982.8 mg/kg in 22-day observation and the 95 % confidence limit was 657.28 -1180.3 mg/kg. The target organ toxicities observed were liver, gall bladder, small intestine (mainly the duodenum), kidney, spleen and testis.

1.2.4.2.2   Acute Oral Toxicity in Beagle Dogs

A GLP acute toxicity study was also conducted in Beagle dogs. Beagles underwent intragastric single administration of AL3818 at the dose of 0, 8.89, 20.0, 67.5, 152.0 and 342.0 mg/kg with 14-day observation. The maximum tolerance dose was 20 mg/kg and the minimum lethal dose was 67.5 mg/kg. The target organ toxicities observed from AL3818 at the DLT level were related to the gastrointestinal tract, heart, liver, kidney, pancreas and thymus gland, adrenal gland, lymph nodes and skin.

1.2.4.3   Repeated-Dose

1.2.4.3.1   Chronic Toxicity in Rats for Thirteen Weeks

A GLP chronic toxicity study was conducted in the rat for 13 weeks of continuous dosing. SD rats were Repeated intragastric administration of AL3818 at the dose of 0.25, 1.0 and 4.0 mg/kg for 13-week with 6-week recovery period. The NOAEL was 0.25 mg/kg and toxic dose was ≥ 1.0 mg/kg. Toxicities of the dental, hepatobiliary system, duodenum, pancreas, adrenal glands, kidneys, blood system. Changes in duodenum, pancreas, adrenal, and kidney were completely recovered after 6-week recovery period and toxicities in hepatobiliary system, teeth and blood system were significantly reduced after 6-week recovery.

1.2.4.3.2   Chronic Toxicity in Beagles For Thirteen Weeks

During this 13-week GLP Toxicology study, Beagles were given repeated intragastric administration of AL3818 at the dose of 0.04, 0.12 and 0.40 mg/kg for 13-week period with 4-week recovery period. At the dose of 0.04~0.40 mg/kg , the added value of Cmax (except for male dogs of day 30) and AUC0-8h is higher than the dose ratio compared with the control group. No drug-related toxicities were found at 0.04 and 0.12 mg/kg in the clinical observation, the average food consumption, body temperature, eye examination, ECG, urine, hematology, coagulation and serum biochemical tests as well as histopathological examination. At 0.40 mg/kg AL3818 results in main toxicities, including: Salivation, vomiting, abnormal vaginal discharge, bloody stools, and gastrointestinal symptoms, slow weight gain and food consumption. These were mainly seen in female Beagle dogs. The main organ toxicities of note were gastrointestinal reactions, slight decrease in heart rate and the function of liver and kidney at the dose of 0.40 mg/kg (AUC_{0-8h} was 195 ng·h/ml) after 13-week administration on Beagle dogs. The NOAEL was 0.12 mg/kg

(AUC$_{0-8h}$ was 51.7 ng·h/ml). Delayed toxicities were not observed and the toxicities were restored after 4-week recovery period.

1.2.4.4   Carcinogenicity

There are no carcinogenicity studies that have been conducted to date.

1.2.4.5   Reproductive Toxicology

An embryo-fetus developmental study was employed to evaluate the reproductive toxicity of AL3818 in Sprague-Dawley (SD) rats. The weight of pregnant rats gained slowly and the rats consumed less food at the dose of 1.8 mg/kg group. The absolute and relative weight of heart and liver from pregnant rats reduced slightly at doses of 0.6 mg/kg and 0.3 mg/kg of AL3818. T h e placental weight reduced in live births, (early stage) fetal absorption increased, post-implantation loss increased, gravid uterus weight reduced, fetal ontogeny was small, the number of birth defects and fetal malformations broods significantly increased. The main deformities observed were edemas showed edema, short-tailed or tailless, and capuchin. The incidence of fetal ventricular dilatation; Fetal caudal vertebrae, sternum, xiphoid, metacarpal and proximal (metatarsal) bone ossification point were reduced, the incidence of fetal part III, IV sternum, skull, lumbar and thoracic dysplasia were increased, and the incidence of rib malformations were increased.

In this experimental condition, AL3818 was administrated intragastric at the stage of pregnancy D6-D15 of SD rats. The embryo-fetal developmental NOAEL was determined to be <0.3 mg/kg.

1.2.4.6   Local Tolerance and Other Studies

No local tolerance or topical studies were conducted with AL3818.

1.2.4.7   Systemic Exposure

The systemic exposure levels of female rats is slightly higher than males (1.5 to 2.3-fold) after intravenous and oral administration, while there are not significant gender differences in the dogs. The CL in the female and male rats is 5.1-7.5 and 3.3-4.1 L/h/kg and the Vss is 18~23 and 34-42 L/kg respectively. The CL in dogs is 0.4 L/h/kg and the Vss is 5.9-6.4 L/kg respectively. The T1/2 in the female and male rats is 4.0-5.3 and 3.0-4.0 h and the T1/2 is 5.4-6.5 h in dogs. The bioavailability (F) of AL3818 in rats is approximately 34% (1.5mg/kg), and 67% in dogs (0.5 mg/kg). There was high protein binding with rat, dog and human plasma for AL3818, which is not limited by drug concentration. The protein binding in rats is 97 %, 96 % in dogs, and 93 % in humans.

1.2.4.8   Toxicology Conclusions

AL3818 selectively inhibits KDR, FGFr and VEGFr with a strong anti-tumor activity in animal models and potentially improved safety profile as compared to sorafenib or sunitinib.

The toxicology of AL3818 was evaluated in mice, rats and dogs. Both acute and chronic (13-week) GLP toxicology studies were conducted with AL3818. The LD50 in mice was determined to be approximately 1735 mg/Kg with 14 days observation and 980 mg/Kg with 22 days observation after oral administration. Based on chronic GLP toxicology evaluations in the rat, the NOAEL for oral administration was determined to be 0.25 mg/Kg and dose limiting toxicities were observed at 4 mg/Kg. The 2 mg/Kg dose was considered the estimated STD-10 in this study with 50% of the animals found dead at the 4 mg/Kg dose and 0% in the 1 mg/Kg dose group. The primary organ toxicities observed in the rat were in the teeth, hepatobiliary system, duodenum, pancreas and kidney, which primarily recovered after a 6-week recovery period. In the dog 13-week GLP toxicology study, the NOAEL was determined to be 0.12 mg/Kg (AUC_{0-8h} was 51.7 ng·h/mL) with primary toxicity at the DLT dose of 0.4 mg/Kg was observed in the gastrointestinal system, liver and kidney. The toxicities observed were recovered 6-weeks after discontinuation of dosing. Thus, the 0.4 mg/Kg dose was considered the HNSTD in the dog.

Based on the estimated STD-10 in the rat of 4 mg/Kg, with conversion for HED (human equivalent dose), the human dose is approximately 0.65 mg/Kg. Taking into account a 1/10th safety factor as recommended by ICH S9 (Guidelines for Non-Clinical Evaluation for Anticancer Pharmaceuticals), a safe starting dose in a human would be defined as 0.065 mg/Kg or approximately 5 mg in a 70 Kg person. If evaluated based on the HNSTD in the dog 13-week GLP dog study the HED is 0.22 mg/Kg, and 1/6th safety factor is 0.037 mg/Kg or 2.6 mg in a 70 Kg person. However, AL3818 has been tested in Phase 1 studies that started at a dose of up to 16 mg per person with tolerable toxicity.

Thus, nonclinical studies completed for AL3818 demonstrate the selective binding to the target receptors and in vivo efficacy in various tumor bearing animal models. The secondary pharmacology and toxicology studies completed to date also confirm that there are relatively lower side effects in animals at efficacious doses as compared to Sorafenib and Sunitinib. These studies support the continued development of AL3818 in long term clinical trials through Phase 3.

Two (2) additional in-vitro genetic toxicology studies were conducted by Hengrui in China according to SFDA regulatory requirements. These studies are considered supportive as translated final reports are not available, but summary information is provided for full disclosure of all known data. Reports on reverse mutation studies confirmed no positive mutagenic response at concentration up to 5,000 μg per plate. Studies to evaluate potential for mutagenesis on CHL cell chromosome aberration at doses up to108 μg/mL did not result in a significant increase in the frequency of chromosomal aberrations compared to negative controls.

1.3   Clinical Experience

Phase I Dose Escalation and PK Trial in Subjects with Advanced Malignancies:

A Phase I clinical trial (NCT01833923) was conducted to determine the tolerance and pharmacokinetics of AL3818 capsules. The main objective of the Phase I clinical trial was the following:

1) Observe safety of AL3818 capsules in human and determine the dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of Anlotinib hydrochloride capsules.
2) Evaluate the pharmacokinetic properties of Anlotinib hydrochloride after oral administration with and without food.

The secondary objective of the clinical trial was the preliminary investigation of the antitumor effect of Anlotinib hydrochloride capsules.

Patients with advanced malignancies were enrolled in the clinical trial. In order to evaluate the efficacy at the same time, patients were to receive the treatment for at least 2 months (56 days).

After oral administration, the gastrointestinal absorption of AL3818 is slow. The plasma pharmacokinetic data of AL3818 after oral administration to rats and dogs demonstrated a slow elimination from the blood compartment. With increasing oral doses, the Tmax in rats showed a trend towards a delayed absorption. Tmax following a low dose (1.5 mg / kg) to rats is approximately 4 hours, following the middle dose (3 mg / kg) to the female rats is 7 hours, male rats is 4 hours, and following the high dose (6 mg/kg) is 5 hours. Tmax values following the different doses (0.5 ~ 3 mg / kg) to dogs is within 3 ~ 5 hours. In the above dose range, the AUC and Cmax (maximum plasma concentration) of AL3818 to rats (0-32 hours) and dogs (0-24 hours) was positively correlated to the dose of oral administration (non-linear correlation). The area under the curve (AUC) correlation coefficient (R^2) of male and female rats is 0.84 to 0.87 and Cmax correlation coefficient (R^2) is 0.74-0.77. The AUC correlation coefficient (R^2) of male and female dogs is 0.83 to 0.97 and Cmax correlation coefficient (R^2) is 0.87-0.91. The systemic exposure levels of female rats is slightly higher than males (1.5 to 2.3-fold) after intravenous and oral administration, while there were not significant gender differences noted in the dogs. The CL in the female and male rats is 5.1-7.5 and 3.3-4.1 L/h/kg and the Vss (volume of distribution at steady state) is 18~23 and 34-42 L/kg respectively. The CL in dogs is 0.4 L/h/kg and the Vss is 5.9-6.4 L/kg respectively. The T1/2 in the female and male rats is 4.0-5.3 and 3.0-4.0 hours and the T1/2 is 5.4-6.5 h in dogs. The bioavailability (F) of AL3818 in rats is approximately 34% (1.5mg/kg) and 67% in dogs (0.5mg/kg). There was high protein binding with rat, dog and human plasma for AL3818, which is not limited by drug concentration. The protein binding in rats is 97 %, 96 % in dogs, and 93 % in humans.

In addition to digestive organs and tissues, the concentrations in most organs of the males at the 4 hour point after oral administration (3 mg / kg) is higher than the adjacent sampling point (1 and 8 hours), while the concentrations in the females at the 8 hour point after oral administration is highest. The tissue concentrations were higher than blood levels at the same time point, there is no

gender difference in tissue distribution of AL3818. The peak concentration in the lung tissue is approximately 184 (males) and 331 (females) times the concentration in the blood at the same time. In the spleen, adrenal gland, large intestine, small intestine, ovary and kidney, the peak concentration is 65~144 times higher than in the blood. In the uterus, heart, liver, stomach, bladder, bone marrow and fat, the peak concentration is 20~47 times higher than in the blood. In skeletal muscle, pancreas, testes and brain, the peak concentration is 17~13 times higher than in the blood.

After oral administration to tumor-bearing nude mice (0.75, 1.5, and 3.0 mg / kg), the AL3818 concentrations in the tissues at 4h point was the highest. The organs AUC of AL3818 was positively correlated with the dose (R2: Liver: 0.95, kidney: 0.90, lung: 0.96, tumor: 0.94, colon: 0.92), and liver tissue AUC is linearly correlated with the dose (R2: 0.95; slope: 0.96; 90% confidence interval: 0.86 to 1.07; 90% confidence interval threshold: 0.84 to 1.16). The highest concentration was in the lung and liver tissues (10 to 14 times higher than in the plasma). The concentration in the kidney was 5.9~8.6 times higher than in the blood. The concentration in the tumor was 2.4~2.6 times higher than in the blood, and the concentration in the colon was 0.8~1.0 times higher than in the blood.

The cumulative effects of AL3818 prototype drugs in the urine (0-72 hours), feces (0-72 hours) and bile (0-24 hours) at a dose of 1.5 mg / kg showed a concentration of 3.4%, 0.7% and 0.6%, respectively, which demonstrated that urine excretion is not the main mode of elimination. AL3818 was not eliminated by excretion in the urine, bile, and there were no gender differences in drug excretion. Drugs were most often eliminated by metabolic transformation, which included oxidation (oxygen plus / plus hydroxyl, dealkylation), glucuronidation, sulfation, etc. There were a total of 23 metabolites detected in rat bile (M1~M14, M16~M24); 16 metabolites were detected in rat urine (M1~M7, M9, M11~M12, M14, M16, M18~M19, M21 and M24); 12 metabolites were detected in rat feces (M1~M2, M9, M11~M12, M14~M15, M18~M19, M21, M23~M24); and 8 metabolites were detected in rat plasma (M6, M11, M14, M16, M18~M19, M21 and M23). M16 (Dealkylation and glucuronidation), M21 (Oxygenase/hydroxylated), and M23 (Oxygenase/hydroxylated) were three main metabolites in plasma. M16, considered the only major metabolite, was the most abundant metabolite in rat urine and bile, and M18 (de-glucuronyl) was the most abundant metabolite in rat feces.

AL3818 demonstrates strong inhibitory activity of human drug-metabolizing enzyme CYP3A4 (IC50 0.0006 μM) , CYP2C9 (IC50 0.25 μM), CYP2C19 (IC50 1.2 μM), CYP2D6(IC50 15 μM) and CYP1A2 (IC50 92 μM). The results indicated that it is important to consider the potential for drug-drug interactions (DDI) between AL3818 and CYP3A4, CYP2C9, CYP2C19 enzyme substrates in clinical trials.

A Phase 1 human clinical trial has been completed in China with AL3818. A Phase 1 dose-escalation safety and PK trial (NCT01833923) was conducted at doses of 5 mg, 10 mg, 12 mg and 16 mg per subject. A total of 34 patients were treated, with 19 subjects having full pK profiles after single dose or at steady state levels. The drug concentration peak time (Tmax) was averaged at 8 (4~10) hours after oral administration of AL3818. Cmax (maximum plasma concentration) was dose

proportional with a peak of 93.1 ng/mL at the 16 mg dose and AUC0-43h was 2212 ng.h/mL. The half-life ($t_{1/2}$) of AL3838 was (80~100 hours). The drug was highly metabolized with urine excretion being less than 1% of administrated dosing.

Based on the pharmacokinetic result of the preclinical animal studies conducted and the pharmacokinetic data of Anlotinib - like drugs (i.e. sorafenib), the time points to collect samples were designed. This pre-experiment was conducted on two subjects in the initial dose group and then according to the results, the original design of the time points to detect drug concentration in the blood was amended.

The dosing regimen for the Phase I clinical trial was as follows:

1) Initial dose level: 5 mg/day QD (n-4) was given with continuous dosing for two cycles of 28 days (56 total days) with each cycle including 21 days dosing and 7 days rest.
2) A 10 mg/day QD (n=4) was given with continuous dosing for two cycles of 28 days (56 total days) with each cycle including 21 days dosing and 7 days rest.
3) A 10 mg QD (n=3) was given with a 21 day treatment cycle that included 14 days of dosing followed by 7 days rest.
4) A 16 mg/day QD (n=3) dose group was treated with a 21 day treatment cycle that included 14 days of dosing followed by 7 days rest. This group reached a DLT and thus a dose reduction was done per protocol.
5) A 12 mg/day QD (n=20) dose group was treated with a 21 day treatment cycle that included 14 days of dosing followed by 7 days rest.
6) A sub-study to evaluate food effect was also done as a 5 mg group given a single dose with a high fat meal (n=6) and empty stomach (n=6).

Administration: Subjects started fasting (water was allowed) from 20:00 the day before the test. At 7:50 on the test day, the blank blood samples were collected. Then at 8:00 Anlotinib capsules were administered orally with 200 mL of warm water. During the test smoking and alcohol were not permitted. In addition, subjects were not permitted to have coffee, carbonated and juice-containing drinks. Strenuous exercise was avoided.

Determination of the drug concentration was performed using HPLC-MS/MS to measure the Anlotinib concentrations in plasma and urine.

The single dose pharmacokinetic parameters of AL3818 are listed below:

Pharmacokinetic parameters	Mean (RSD%)		
	10 mg/subject (n=4)	12 mg/subject (n=11)	16 mg/subject (n=4)
C_{max} (ng/ml)	6.07 (45.2)	11.3 (32.7)	16.1 (12.7)
C_{max}/Dose	43.4 (45.3)	64.6 (34.9)	57.6 (8.65)
T_{max} (h; p.o)	6.75 (50.4)	8.73 (69.3)	10.0 (95.2)
AUC_{0-th} (ng·h/ml)	327 (31)	938 (33.1)	1328 (25.9)
AUC/Dose	2300 (19)	5401 (37)	4710 (15)
$AUC_{0-\infty}$ (ng·h/ml)	570 (36)	1164 (34)	1719 (25.4)
$t_{1/2}$ (h)	88.9 (22)	92.0 (13.3)	96.7 (15.0)
MRT (h)	142 (20)	162 (26)	163 (20.5)

The drug concentration peak time (T_{max}) was averaged at 8 (4~10) hours after oral administration of *AL3818* capsules. The maximum drug blood concentration (C_{max}) and area under the curve (AUC) tended to increase following each dose increase in a slightly greater than proportional manner. Half-life ($t_{1/2}$) of *AL3818* was (80~100h). Urine excretion was less than 1 % of administrated dosing. The drug blood concentration was around 1/10 of maximum drug blood concentration (C_{max}) 240 hours (10 days) after administration.

For continuous dosing pharmacokinetics the study was started for patients who met the guidance by administrating *AL3818* capsule once and single dosing analysis was performed. The continuous dosing study was started after at least a seven day wash out period. Subjects were dosed by continuous daily treatment for two weeks and then resting for one week as one cycle of therapy. At least two cycles of therapy were monitored as part of this trial. Five dosing groups (5 mg fasted, 5 mg with a high fat meal, 10 mg fasted, 12 mg fasted and 16mg fasted) with a total of 34 patients were administrated orally with *AL3818* capsule and were analyzed for drug blood concentrations.

Figure 1.3-1: Single Dosing and Continuous 2wks rest 1wk dosing Plasma Exposures
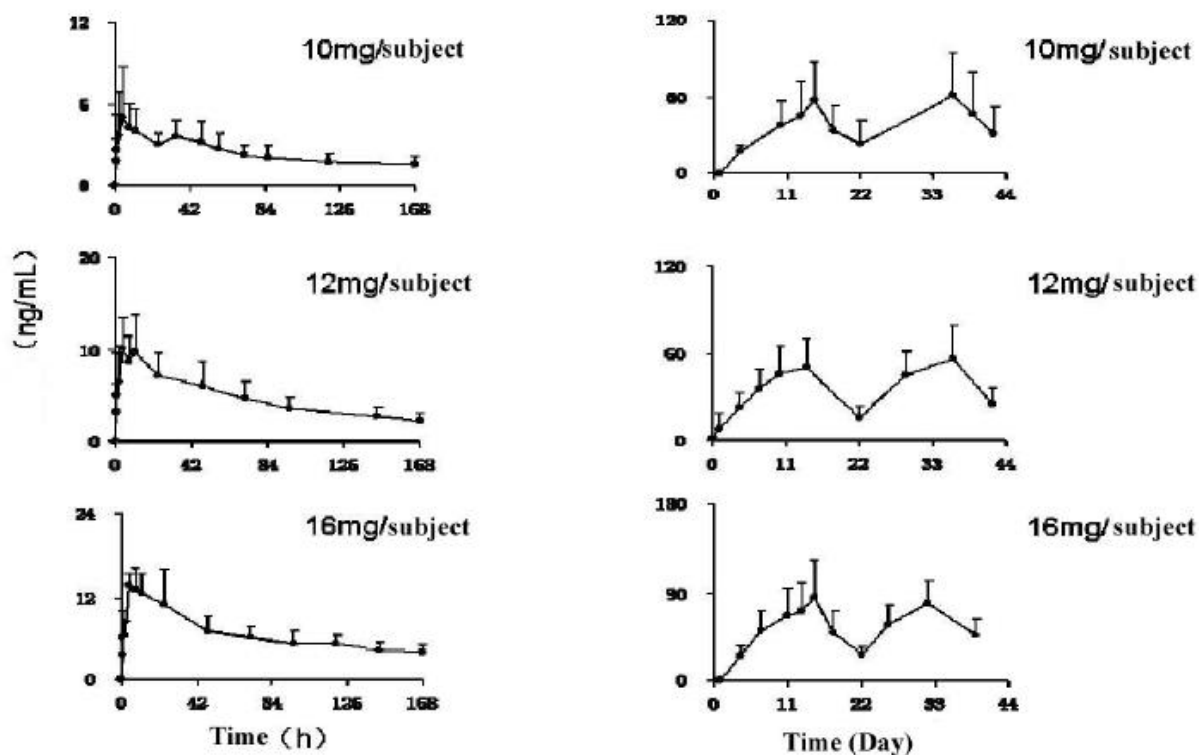
Table 1.3-1: Calculated Pharmacokinetic Parameters of Continuous 2wks Rest 1wk Dosing

Pharmacokinetic Parameters	Mean （RSD%）		
	10 mg/subject （n=3）	12 mg/subject （n=15）	16 mg/subject （n=3）
C_{max} (ng/mL)	64.9 (44.5)	67.0 （29.0）	93.1 (29.3)
C_{max} /Dose	388 （45）	361 （32）	300 (31)
$AUC_{0-43 天}$ (ng·h/mL)	1545 (56)	1500 （27）	2212 (35)
AUC/Dose	9234 (56)	8272 （32）	7109 (36)

Continuous dosing of Anlotinib appears to cause drug accumulation in blood as expected given the long half-life. In order to adopt the regimen for continuous therapy given the long half-life of the drug, the dosing regimen was adjusted to 2 weeks dosing and 1week rest to reach peak drug concentration at Day 14 followed by a recovery period. The drug concentration can be managed under 100 ng/ml in the following treatment dosing so that the drug accumulation can be well controlled.

Pharmacokinetics to study the effects of diet with healthy volunteers was conducted. The random, double cycles and self-cross design was used for 12 (age 18-40) healthy volunteers who were randomly separated into two groups (empty stomach and fat meal) with 6 subjects in each group (half male/female). Both groups were administered with *AL3818* capsule 5mg after no food for 10 hours. Both subjects in each group were then switched and administered the same dose after a 28 days non-dosing period.

The comparison of pharmacokinetic parameters of the empty stomach group with the fat meal group is provided in following chart. The fat meal group tends to have peak drug concentration delayed with decreased absorption of the drug (80% of empty stomach). This difference was not considered significant and dosing may be done with or without food.
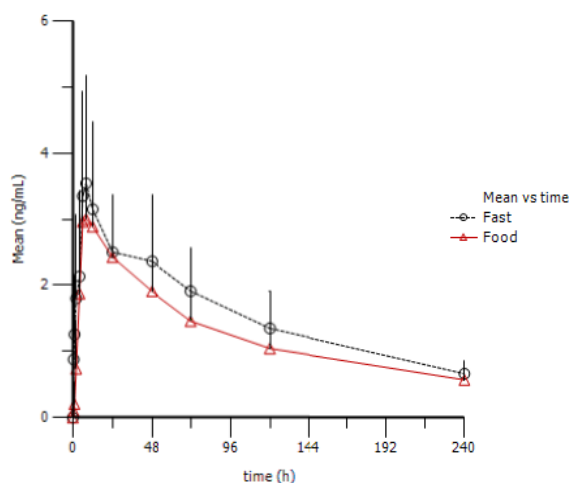
PK Parameters	Fat Meal	Empty Stomach
C_{max} $(ng\cdot mL^{-1})$	3.23 ± 1.30	3.81 ± 1.59
T_{max} (h)	11.2 ± 6.4	8.3 ± 2.4
$AUC_{inf}/AUC_{0-\infty}$ $(ng\cdot h\cdot mL^{-1})$	408 ± 122	486 ± 150
$MRT_{inf}/MRT_{0-\infty}$ (h)	171.5 ± 47.6	165.7 ± 36.3
$t_{1/2}$ (h)	120.0 ± 31.8	116.1 ± 27.3

1.3.1 Overview of Clinical Pharmacology

Clinical Pharmacology data was not collected in this study.

1.3.2 Overview of Efficacy

Up to 4 July 2013, there were a total of n=34 patients enrolled in the Phase I clinical trials and treated with multiple doses of AL3818. Four subjects were treated at 5 mg/day and thirty at 10 mg/day or greater. Based on evaluation of the higher dose group subjects there was one PR

(3.3 %), twenty-three (23) SD (76.7 %), and five PD (16.7 %) results. Subjects were evaluated for safety for the first two cycles as part of the clinical study report, with follow up compassionate use treatment for between 4 and 26 days after the primary safety evaluation period.

For treatment time in the 10 mg/day or greater dose groups, there were two patients treated for more than 72 weeks, two treated for more than 48 weeks, nine treated greater than 24 weeks and two treated or more than 12 weeks. The average treatment cycles were at 8.7. The results of these 30 patients were: n=1 no target lesion, n=1 non target lesion and 28 patients tumor changes are in the following chart:

Figure 1.3-2:Anlotinib Hydrochloride Phase I Clinical Trial Patient Best Efficacy
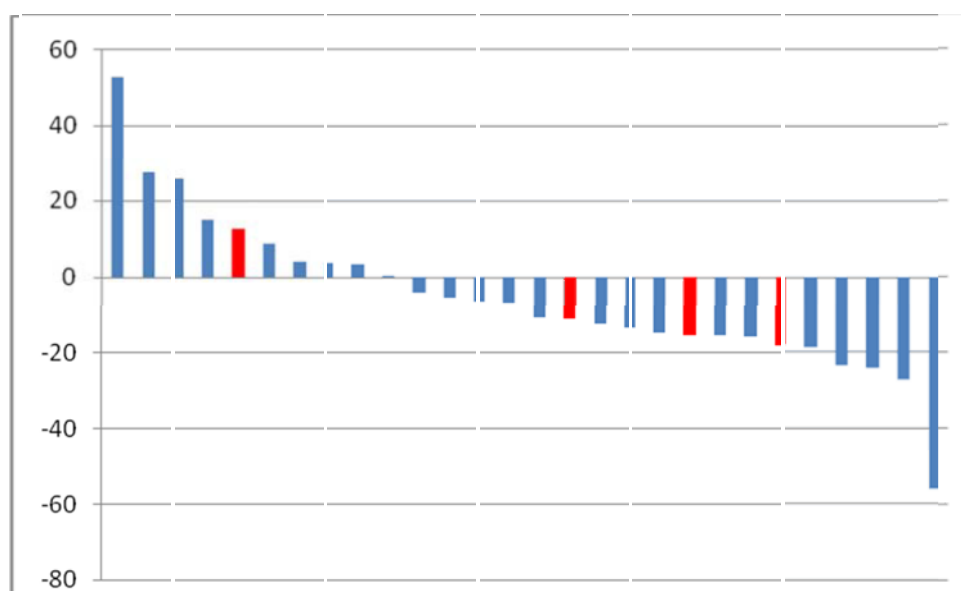
Patients Tumor Size Changing Results [(Measuring Best Value-Baseline)/Baseline (n=28)]

Preliminary efficacy analysis based on tumor types is provided in the following tables

Table 1.3-2: Soft tissue sarcoma

No	Tumor Type	Dose (mg/d)	Cycle	Response
1	Alveoli Soft Tissue	5	C2	PD
7	Alveoli Soft Tissue	10--12	C25	SD (Small-Large)
10	Liposarcoma	10	C4	SD (Large)
13	Alveoli Soft Tissue	16--12	C22	SD (Small)

No	Tumor Type	Dose (mg/d)	Cycle	Response
16	Malignant Fibrous Histiotoma	12	C14	SD (Small)-PR
17	GIST	12	C6	SD (Large)
25	Epithelioid Hemangioendothelioma	12	C2	PD
31	Rhabomyosarcoma	12	C2	PD

Table 1.3-3: Medullary Thyroid Carcinoma (MTC)

No	Tumor Type	Dose (mg/d)	Cycle	Response
18	MTC	12	C5	SD (small)
19	MTC	12	C13	SD (small)
20	MTC	12	C15	SD (small)
21	MTC	12	C13	SD (small)
24	MTC	12	C14	Clinical Benefit *
26	MTC	12	C2	PD

*from calcitonin level to determine   #liver metastasis

Table 1.3-4: Non-small Cell Lung Cancer (NSCLC)

No	Tumor Type	Dose (mg/d)	Cycle	Response
9	NSCLC	10	C26	SD (small)
15	NSCLC (adenocarcinoma)	12	C16	SD (small)
23	NSCLC (adenocarcinoma)	12	C12	SD (small)
28	NSCLC (adenocarcinoma)	12	C6	SD (small)

In summary, AL3818 capsule has good tolerability and clinical efficacy for many patients at 12 mg/day with 2 weeks dosing followed by 1 week recovery regimen.

AL3818 capsule had good responses in soft tissue sarcoma, medullary thyroid carcinoma and NSCLC (include SD small), rated close to 80 %, which provide a reliable basis for moving to phase II clinical trial. Tolerability and preliminary efficacy studies of some RCC and liver cancer patients are on-going.

1.3.3   Overview of Clinical Safety

A Phase I clinical trial (*NCT01833923)* was conducted to determine the tolerance and pharmacokinetics of AL3818 capsules.

The original clinical design for tolerability study was 28 day dosing as one cycle with 21 days of treatment with AL3818 and 7 days off therapy, with at least two cycles continuous dosing for safety evaluation.

The initial dosing at 5 mg QD and 10 mg QD for four patients each group were conducted with the 28 day cycle of therapy. Due to Grade (G) 3 hypertension and abnormal liver function observed as well as drug accumulation in blood, the treatment cycle was reduced to a 21-day cycle with 14 days dosing and 7 days rest.

Subsequent cohorts were enrolled based on the amended protocol with two (2) weeks continuous dosing followed by one (1) week rest without dosing for a total of three weeks (21 day) which is one cycle and at least two cycles (42 days) were required for safety evaluation and dose escalation.

The third cohort of four patients was administered 10mg/day QD for 21 day cycles and evaluated after two complete cycles of treatment. There were no significant adverse events observed. The forth cohort of three patients was administered 16mg/day QD for 21 days. One patient was discontinued after Day 40 (Day 12 of cycle 2) due to G3 fatigue. A second patient was discontinued at the end of cycle 2 (Day 42) due to G3 hypertension. These two events were SAEs and considered a DLT based on the protocol definition. Thus, two of three subjects in this cohort reached a dose that was considered intolerable, possibly due to accumulation of drug after two cycles of treatment.

The fifth cohort was given 12 mg/day QD for two 21 day cycles, each with 14 days dosing and 7 days rest. A larger group of twenty (20) patients was enrolled to use to obtain a more accurate assessment of safety and confirm this dose as the MTD.

1.3.3.1   Extent of Exposure

All 34 subjects evaluated for safety received multiple doses of study medication as part of this study with at least one full cycle of treatment. The safety analysis and comparison of dose groups was conducted for the first two cycles of therapy.

Up to July 3, 2013, There are 34 patients have been grouped: 5 mg/day at n=4; 10 mg/day at n=4; 10 mg/day 2 wks dosing/1 wk. resting at n=3; 16 mg/2 wks dosing/1 wk. resting at n=3; 12 mg/2 wks dosing/1 wk. resting at n=20. Subjects who tolerated the therapy well were allowed to extend treatment with dosing cycles in the 12 mg/day QD group from 4 to 26 cycles of therapy (14 days treatment and 7 days off therapy). One additional subject (total n=35) was enrolled after the end of the study for compassionate use reasons, but their data is included in the summary of adverse events below.

1.3.3.2   Adverse Events

1.3.3.2.1   Brief Summary of Adverse Events

The summary tables show TEAE (treatment-emergent adverse event) data presented as n (%), where n is the number of subjects to experience that TEAE, and (%) is the percentage of subjects within the defined group to experience that TEAE. Subjects who experienced the same TEAE more than once were only counted once for that event.

Overall, 35 subjects (100%) reported at least 1 TEAE. The highest percentage of subjects reported TEAEs classified in the SOC (Standard Occupational Classification) of blood disorders (e.g. elevated triglycerides or elevated ALT or AST) or cardiovascular disorders (e.g. elevated blood pressure). The most frequently reported TEAEs were elevated triglycerides (16 subjects, 45.7 %), hypertension (13 subjects, 37.1 %), and elevated ALT or AST (12 subjects, 34.3 %).

These events were all considered to be expected based on the known pharmacology of AL3818 and other multi-kinase inhibitors.

A total of 2 (5.7 %) subjects reported 2 SAEs during the period of this safety analysis (first two cycles) with 4 subjects (11.4 %) reporting an SAE taking into account all long term follow up data. Both subjects who experience SAEs during the first two cycles of therapy (safety evaluation period) were enrolled in the 12 mg/day QD dose group with 21 day cycle of therapy. Both events (abdominal pain and pneumothorax) resolved. Two adverse events meeting the criteria of a DLT were also reported at 16 mg/day QD dose group during the second cycle of dosing. Both DLT events did not meet the criteria to classify them as an SAE, but were still considered dose limiting. One DLT was Grade 3 fatigue and the other was Grade 3 hypertension.

1.3.3.2.2   Displays of Adverse Events

1.3.3.2.2.1   Displays of TEAEs

Summary safety data is reported as part of this safety analysis as of the data cutoff date of 03 July 2013. A summary of TEAEs at the treatment level is presented in Table 1.3-5.

Table 1.3-5: **Summary of Treatment-Emergent Adverse Events on Treatment (First Two Cycles of Treatment)**

Event Term	5 mg QD 28d Cycle (N=4) n (%)	10 mg QD 28d Cycle (N=4) n (%)	10 mg QD 21d Cycle (N=3) n (%)	12 mg QD 21d Cycle (N=21) n (%)	16 mg QD 21d Cycle (N=3) n (%)
Subjects with at least one TEAE in first 2 cycles	4 (100%)	4 (100 %)	3 (100 %)	21 (100 %)	3 (100 %)
Elevated ALT or AST	1 (25 %)	1 (25 %)	--	9 (42.9 %)	1 (33 %)
Elevated bilirubin	1 (25 %)	--	--	5 (23.8 %)	--
Elevated triglycerides	3 (75 %)	4 (100 %)	--	7 (33.4 %)	2 (67 %)
Hypertension	1 (25 %)	4 (100 %)	1 (33 %)	6 (28.6 %)	1 (33 %)
Hyperthyroidism	--	1 (25 %)	--	2 (9.5 %)	2 (67 %)
Hypothyroidism	--	--	--	8 (38.1 %)	--
Hand and Foot Syndrome	--	1 (25 %)	--	4 (19 %)	--
Diarrhea	--	2 (50 %)	1 (33 %)	6 (28.6 %)	--
Elevated fat, amylase	--	--	1 (33 %)	2 (9.5 %)	1 (33 %)
Fatigue	--	--	1 (33 %)	5 (23.8 %)	1 (33 %)
Hoarseness	--	--	2 (67 %)	3 (14.3 %)	1 (33 %)
Bleeding	--	--	--	--	1 (33 %)
Rash	--	--	--	4 (19 %)	--
Increase creatinine	--	--	--	1 (4.8 %)	--
Increased Cholesterol	--	--	--	5 (23.8 %)	--
Increased LDL	--	--	--	4 (19 %)	--
Decrease WBC	--	--	--	3 (14.3 %)	--
Albuminuria	--	--	--	5 (23.8 %)	--
Urine occult blood	--	--	--	5 (23.8 %)	--
Lipase	--	--	--	2 (9.6 %)	--
Elevated Myocardial Enzyme	--	--	--	2 (9.5 %)	--
pneumothorax	--	--	--	1 (4.8%)	--
Abdominal pain	--	--	--	1 (4.8%)	--
Toothache	--	--	--	1 (4.8%)	--
Sore muscle	--	--	--	3 (14.3%)	--
Sore throat	--	--	--	1 (4.8%)	--
Dizziness	--	--	--	1 (4.8%)	--
Headache	--	--	--	1 (4.8%)	--
Chest pain	--	--	--	1 (4.8%)	--

Event Term	5 mg QD 28d Cycle (N=4) n (%)	10 mg QD 28d Cycle (N=4) n (%)	10 mg QD 21d Cycle (N=3) n (%)	12 mg QD 21d Cycle (N=21) n (%)	16 mg QD 21d Cycle (N=3) n (%)
Pain	--	--	--	1 (4.8 %)	--
Fever	--	--	--	1 (4.8 %)	--
Gum infection	--	--	--	1 (4.8 %)	--

1.3.3.2.2.2   TEAEs by Severity

The majority of TEAEs events reported by subjects were Grade 1 or 2 in severity, with only 5 subjects reporting events that were Grade 3 in severity during the safety reporting period (first two cycles of treatment).

Total events classified as TEAEs are summarized by severity are summarized in Table 1.3-6.

Table 1.3-6: Summary of TEAEs by Severity

Event Term	10 mg QD 21d Cycle (N=3) n (%)		12 mg QD 21d Cycle (N=21) n (%)		16 mg QD 21d Cycle (N=3) n (%)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Subjects with at least one TEAE	3 (100 %)	1 (33 %)	21 (100 %)	2 (9.5 %)	3 (100 %)	2 (67 %)
Elevated ALT or AST	--	--	9 (42.9 %)	--	1 (33 %)	--
Elevated bilirubin	--	--	5 (23.8 %)	--	--	--
Elevated triglycerides	--	--	7 (33.4 %)	1 (4.8%)	2 (67 %)	--
Hypertension	1 (33 %)	--	6 (28.6 %)	--		1 (33 %)
Hyperthyroidism	--	--	2 (9.5 %)	--	2 (67 %)	--
Hypothyroidism	--	--	8 (38.1 %)	--	--	--
Hand and Foot Syndrome	--	--	4 (19 %)	--	--	--
Diarrhea	1 (33 %)	--	6 (28.6 %)	--	--	--
Elevated fat, amylase		1 (33 %)	2 (9.5 %)	--	1 (33 %)	--
Fatigue	1 (33 %)	--	5 (23.8 %)	--	--	1 (33 %)
Hoarseness	2 (67 %)	--	3 (14.3 %)	--	1 (33 %)	--
Bleeding	--	--	--	--	1 (33 %)	--
Rash	--	--	4 (19 %)	--	--	--
Increase creatinine	--	--	1 (4.8 %)	--	--	--

Event Term	10 mg QD 21d Cycle (N=3) n (%)		12 mg QD 21d Cycle (N=21) n (%)		16 mg QD 21d Cycle (N=3) n (%)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Increased Cholesterol	--	--	5 (23.8 %)	--	--	--
Increased LDL	--	--	4 (19 %)	--	--	--
Decrease WBC	--	--	3 (14.3 %)	--	--	--
Albuminuria	--	--	5 (23.8 %)	--	--	--
Urine occult blood	--	--	5 (23.8 %)	--	--	--
Lipase	--	--	2 (9.6 %)	1 (4.8 %)	--	--
Elevated Myocardial Enzyme	--	--	2 (9.5 %)	--	--	--
Pneumothorax	--	--	--	1 (4.8 %)	--	--
Abdominal pain	--	--	--	1 (4.8 %)	--	--
Toothache	--	--	1 (4.8 %)	--	--	--
Sore muscle	--	--	3 (14.3 %)	--	--	--
Sore throat	--	--	1 (4.8 %)	--	--	--
Dizziness	--	--	1 (4.8 %)	--	--	--
Headache	--	--	1 (4.8 %)	--	--	--
Chest pain	--	--	1 (4.8 %)	--	--	--
Pain	--	--	1 (4.8 %)	--	--	--
Fever	--	--	1 (4.8 %)	--	--	--
Gum infection	--	--	1 (4.8 %)	--	--	--
Delirium	--	--	--	1 (4.8 %)	--	--

1.3.3.3 Analysis of Adverse Events

No statistical analyses of AEs were performed in this study. Safety data is presented as summary statistics.

1.3.3.4 Deaths, Other SAEs, and Other Significant AEs

1.3.3.4.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

1.3.3.4.1.1 Deaths

No deaths were reported during the safety evaluation period that included the first two cycles of therapy in each cohort.

1.3.3.4.1.2 Other Serious Adverse Events and DLT Events

At the time of this safety analysis data cut off (4 July 2013) there were only 2 SAEs (5.7 %) reported in 35 subjects during the first two cycles of treatment (safety reporting period). Both of these SAEs were considered at least possibly related to study medication and considered DLT events in the trial.

Two additional SAEs were reported in long-term follow up therapy of subjects. A summary of all SAEs reported in the two cycle safety review period and long term follow up period is provided in Table 1.3-7.

Table 1.3-7: Summary of All SAEs on Treatment (All Dosed Subjects)

SAE Term	All Subject (N=35) n (%)	5 mg/day QD Dose Group (N=4) n (%)	12 mg/day QD Dose Group (N=21) n (%)
Subjects with at least one SAE	4 (11.4 %)	1 (14.3 %)	3 (14.3 %)
increased ALT、AST	1 (2.9 %)	1 (14.3 %)	
abdominal pain	1 (2.9 %)		1 (4.8 %)
pneumothorax	1 (2.9 %)		1 (4.8 %)
delirium	1 (2.9 %)		1 (4.8 %)

There were two DLT events at the 16 mg/day QD dose that did not meet the criteria for a DLT. One event was Grade 3 fatigue that did not subside. The second event was Grade 3 hypertension that could not be managed with medication well.

Table 1.3-8: Summary of All DLT Events First Two Cycles (All Dosed Subjects)

DLT Term	All Subject (N=35) n (%)	16 mg/day QD Dose Group (N=3) n (%)
Subjects with at least one DLT	2 (5.7 %)	2 (67 %)
fatigue	1 (2.9 %)	1 (33 %)
hypertension	1 (2.9 %)	1 (33 %)

1.3.4 Benefits and Risks Conclusions

Up to July 3, 2013, 34 patients have been treated as follows: 5 mg/day at n=4; 10 mg/day at n=4; 10 mg/day 2 wks dosing/1 wk. resting at n=3; 16 mg/2 wks dosing/1 wk. resting at n=3; 12 mg/2 wks dosing/1 wk. resting at n=20 (n=11 were off the group). Subjects who tolerated the therapy well were allowed to extend treatment with dosing cycles in the 12 mg/day QD group from 4 to

26 cycles of therapy (14 days treatment with AL3818 and 7 days off of AL3818). Thus, the 12 mg/day QD dose appeared to be confirmed as the MTD.

Overall, the 12 mg/day QD dose with a 21 day treatment cycle was well tolerated and subjects continued therapy long term for up to 26 cycles at the time of this safety analysis. Serious events were limited to the 16 mg/day QD group only, with 2 (9.5%) of subjects reporting an SAE during the first two cycles of therapy.

2.0 PURPOSE AND STUDY OBJECTIVES

2.1 Purpose

The primary objective of this study is to investigate the safety and efficacy of adding oral AL3818 to standard platinum-based chemotherapy, concurrently and continued as a maintenance therapy for up to 18 months, in subjects with recurrent or metastatic endometrial, ovarian or cervical cancer.

2.2 Study Objectives

2.2.1 Primary Objective

The Primary Objectives of this study are:

Part 1: Phase 1 Portion

- The primary objective of this study is to investigate the safety and tolerability of adding oral AL3818 to standard platinum-based chemotherapy with carboplatin and paclitaxel in subjects with recurrent or metastatic endometrial, ovarian or cervical cancer.

Part 2: Phase 2a Portion

- To obtain data on objective response rates in subjects with recurrent or metastatic endometrial, ovarian or cervical cancer treated with AL3818 given concurrently with carboplatin and paclitaxel chemotherapy and continued as maintenance treatment for up to 18 months.

2.2.2 Secondary Objectives

The Secondary Objectives of this study are as follows:

Part 1: Phase 1 Portion
- Determination of MTD in the study population.

Part 2: Phase 2a Portion
- To obtain data on overall survival (OS) rates in subjects with recurrent or metastatic endometrial, ovarian or cervical cancer treated with AL3818.
- Toxicity
- Quality of Life (QoL)

3.0   STUDY DESIGN

3.1   Description of Trial Design

This protocol will be divided into two parts: Part 1 will evaluate the safety and tolerability of adding oral AL3818 to standard platinum-based chemotherapy in continuous 21-Day cycles; Part 2 will evaluate the safety and preliminary efficacy of adding oral AL3818 at the MTD from Part 1 of this study to carboplatin and paclitaxel chemotherapy and continued as maintenance therapy for up to 18 months. All subjects in Part 1 and Part 2 of this study will be permitted to continue therapy with only safety monitoring and bimonthly assessments for progression, if AL3818 is well tolerated and the subject has stable disease or better.

Up to 48 subjects will be enrolled in this clinical trial (Possibly up to 54).

Part 1 Dosing Procedure:

Part 1 will include a sequential evaluation of 3 subjects per cohort up to 3 subjects in total. Cohort 1 will initiate at a dose of 12 mg AL3818 (administered on Day 8 of each cycle for a 7 days off and 14 days on AL3818 schedule) combined with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) plus paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle), for six cycles of 21 days. After three subjects have completed one cycles of therapy without a DLT then Part 2 may begin. All subjects will be allowed continuation of therapy with repeat cycles of 21-days if they are tolerating AL3818 and have stable disease or better.

Subjects in Part 1 will initially be given a single dose of AL3818 on Day 8 (7 days off, 14 days on AL3818) at the clinic 7 days after chemotherapy treatment with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) and paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle). The subject will be maintained in the clinical unit for approximately 8 hours after dosing for monitoring. Subjects will then be discharged if there are no significant clinical events and continue therapy daily for the next five 21-day dosing cycles (7 days off, 14 days on AL3818). Subjects will return to the site on Days 15, 22, 29, 43, 64, 85 and 106 of therapy for safety evaluations. On Days 8 and 15, the subject will be dosed in the clinic during the safety evaluation.

Each subject in Part 1 will subsequently be allowed to continue additional 21-day cycles. (See Appendix A1). If the subject is tolerating AL3818 well and at least stable disease by radiographic assessments, they may continue on 21-day cycles of therapy as described in Appendix A3.

Subjects will be assessed for disease progression after six complete 21-day cycles of therapy in Part 1. Patients may continue on therapy for additional 21-Day cycles if the therapy is well tolerated. Efficacy assessments and disease progression (RECIST imaging) will be assessed every six 21-Day cycles. If study medication is discontinued for any reason the subjects will be assessed for safety for at least 21-Days after the last dose of AL3818.

For Part 1 of this study, a Dose Limiting Toxicity (DLT) event is defined as any of the following events that are assessed by the Investigator as probably or possibly related to AL3818 and occur during or after the initial dose on Day 8 through Day 21 of the first cycle of therapy.

1. CTCAE Grade 4 event

2. Grade 3 thrombocytopenia with bleeding

3. Grade 3 non-hematologic toxicity, including Grate 3 nausea, vomiting, diarrhea and hypertension that continues more than 72 hours despite optimal medical management (Note: The prophylactic use of antihypertensive agents for Grade 1and Grade 2 hypertension in order to minimize the occurrence of more severe or persistent hypertension while undergoing treatment with AL3818 does not constitute a Grade 3 toxicity)

4. Grade 3 ALT or AST lasting >7 days, based on Hy's Law criteria

5. Grade 3 febrile neutropenia (<1,000 neutrophils/mm^3)

6. Grade 3 hematologic toxicity with duration > 7 days

If a DLT is experienced in any cohort, the cohort will be expanded to 6 subjects and the dose of AL3818 will be lowered to 10 mg. If at 10 mg a DLT is experienced, the dose of AL3818 will be lowered to 8 mg and so on for each DLT experienced. If two (2) DLTs are experienced in any cohort, the study will be paused until the safety events are evaluated.

The maximum tolerated dose (MTD) will be defined as the dose level below that where 2 DLTs are experienced.

For subjects in this study who have stable disease (SD) or better and are tolerating therapy well, treatment with AL3818 may continue for additional 21-day cycles of therapy until disease progression, intolerable side effects are experienced or withdrawal of consent.

Table 3.1-1: Primary Study Design: Part 1

Screening/ Baseline	Dosing Period			Extension
	Dose	Primary Safety Evaluation	Efficacy* Evaluation	
Days -14 to -1	Chemotherapy Day 1 of each cycle AL3818 Days 8 to 21	Days 8 to 21 (first cycle) then every 21 days up to Day 126	Day 63 and Day 126	Extension beyond Day 126 is permitted with an additional 21-Day cycles until progression, significant side effects or withdrawal of consent

*In Part 1, Day 126, efficacy measures are considered biomarker and radiographic Imaging assessment.

Part 2 Dosing Procedures:

Part 2 of this study will include up to 45 additional subjects with metastatic endometrial cancer (approx. 15), ovarian cancer refractory to platinum therapy (approx. 15) or cervical cancer refractory to standard therapy (approx. 15). Each subject will receive a dose of up to 12 mg AL3818 (administered on Day 8 of each cycle for a 7 days off and 14 days on AL3818 schedule) or a maximum of the MTD from Part 1 of this study combined with carboplatin (AUC 5 over approximately 30 minutes given on Day 1 of each cycle) and paclitaxel (175 mg/m^2 over approximately 3 hours given on Day 1 of each cycle) for six continuous 21-Day cycles of therapy and continued as maintenance therapy for up to 18 months. For cervical cancer, cisplatin (recommended dose of 75 mg/m^2 would be preferred over carboplatin. If a subject experiences an intolerable side effect, a dose reduction or a dose interruption is allowed at the discretion of the investigator as described in Section 3.4.4 and 3.4.5. Subjects will be evaluated by RECIST (version 1.1) response at the end of each third cycle of therapy of Part 2 of the study. Safety reporting will be continued for 21-Days from the last dose of study medication if discontinued for any reason. During Part 2 any subject experiencing an adverse event that is consistent with the DLT criteria above will be considered an SAE and reported to the Medical Monitor who will assess the case. If two similar events are reported, new enrollment in the study will be stopped until the medical monitor can evaluate safety.

All subjects in Part 1 and 2 of this trial will be eligible to continue therapy provided they have a least stable disease or better and are, in the opinion of the investigator, adequately tolerating treatment with AL3818.

3.2   Study Endpoints

3.2.1   Primary Endpoint

The primary endpoint in Part 1 of this trial is evaluation of dose limiting toxicity (DLT) and general safety during six continuous 21-day cycles of carboplatin and paclitaxel chemotherapy (Administered on Day 1 of each cycle) combined with AL3818 (7 days off, 14 days on AL3818 therapy schedule). The assessment will be governed by the DLT criteria. Additional safety variables to be evaluated in this study are adverse events, physical examination findings, vital signs (specifically including blood pressure), clinical laboratory evaluations including serum chemistry, hematology (including RBC morphology and reticulocyte count), urinalysis (with detailed sediment analysis, proteinuria, and electrocardiogram (ECG). These variables will be evaluated at the time points indicated in Section 1 and Appendix A.

In Part 2 of this study the primary endpoint will be the Objective Response Rates in subjects with recurrent or metastatic endometrial cancer, recurrent ovarian or recurrent cervical cancer treated with AL3818 given concurrently with carboplatin and paclitaxel chemotherapy and continued as maintenance treatment for up to 18 months evaluated by the RESIST (version 1.1) criteria. For cervical cancer, cisplatin would be preferred over carboplatin.

3.2.2   Secondary Endpoints

The key secondary endpoints of the study are as follows:

- In Part 1, Determination of MTD.

- In Part 2 of this study, Overall Survival (OS) Rates, Toxicity and Quality of Life (QoL).

Other secondary endpoints include:

- Possibly acquire pharmacodynamic endpoints will include specific tumor markers for the target cancers that include levels of FGFR2.

3.3   Measures to Minimize Bias

3.3.1   Blinding

This study is not randomized and has no concurrent controls. Study drug will be administered in an open-label fashion.

3.3.2   Assignment to Study Drug

Each subject who is determined to be eligible for the study will be assigned, via facsimile or e-mail transmission, a unique treatment number consisting of a three-digit subject number (XXX) by the Medical Monitor after confirming patient eligibility. Each subject will be assigned to a cohort based on the order of entry into the study.

Subject numbers will be consecutive such that the three digit number ("XXX") is continuous for each patient enrolled into the trial.

Prior to enrollment of any subject, the subject enrollment form will be completed and sent to the ADVENCHEN Deputy Clinical Director at dougc@advenchen.com or to Dr. Zhisong Cao at zhisongc@advenchen.com. The Deputy Clinical Director will review the patient information and eligibility to confirm acceptability to enroll the subject. The Deputy Clinical Director will assign the sequential subject number and send the approved enrollment form with the patient number to the investigator or designee.

3.4 Study Drugs

3.4.1 Rationale for Doses and Dosing Regimen

The platinum-based chemotherapy agents are not being investigated and are not provided as part of the patient's trial drug.

A starting dose of 12 mg of AL3818 administered as a single oral administration on Day 8 of each 21-Day cycle has been selected based on the available clinical data from a completed Phase 1 study that demonstrated this dose was tolerable and based on nonclinical GLP 13-week toxicology.

In Part 1, three subjects will be enrolled at a dose of 12 mg AL3818 (Administered on Day 8 of each cycle on a 7 days off, 14 days on schedule) combined with carboplatin and paclitaxel. In Part 2 subjects will receive a dose of up to 12 mg AL3818 (Administered on Day 8 of each cycle on a 7 days off, 14 days on AL3818 therapy schedule) or a maximum of the MTD from Part 1 of this study combined with carboplatin and paclitaxel.

All doses of AL3818 will be given once daily in the fasted state at least 30 minutes prior to a meal or 2 hours after a meal. If a subject experiences gastrointestinal side effect, they may take the product with a light meal, milk or yogurt. A light meal is defined as a low fat meal or snack, typically no more than 400 kcal and comprising of less than 25 % fat and less than 20 % protein.

A dose reduction may be allowed in any cohort if the subject does not experience a DLT, but side effects are intolerable at any time during therapy.

3.4.2 Dosages and Dosing Regimen

3.4.2.1 21-Day Course

For Part 1: Subjects will be administered carboplatin (AUC 5 over approximately 30 minutes) and paclitaxel (175 mg/m^2 over approximately 3 hours) on Day 1 of each cycle. Subjects will then receive AL3818 by oral administration on Day 8 in the clinic (7 days off, 14 days on AL3818 therapy schedule). If no significant safety events occur (see Section 3.4.3), the same dose will be continued once daily for six (6) 21-Day cycles of therapy beginning with 7 days of

rest (Chemotherapy administered on Day 1 then AL3818 on Day 8) and 14 days of active dosing of AL3818.

For Part 2: Subjects will be administered carboplatin (AUC 5 over approximately 30 minutes) and paclitaxel (175 mg/m^2 over approximately 3 hours) on Day 1 of each cycle. Subjects will then receive AL3818 by oral administration on Day 8 in the clinic. Treatment will be administered once daily for six (6) 21-Day consecutive cycles of therapy beginning with 7 days of rest (chemotherapy on Day 1 then AL3818 on Day 8) and 14 days of active dosing of AL3818.

3.4.2.2 Additional 21-Day Courses (Continuation of Therapy)

In the absence of any significant side effects, and in the case of stable disease or better, a subject may continue to receive AL3818 at the same dose and regimen (See Appendix A3 for schedule of compassionate use treatment cycles).

Section 3.4.6 describes criteria for Dose Interruptions and a discussion of procedures to follow for events meeting Grade 3 or 4 toxicity criteria.

Table 3.4-1: AL3818 Dose Cohorts

Coh	Number of Subjects*	AL3818
1	3	12 mg
2 (Possibly)	3	10 mg
3 (Possibly)	3	8 mg
Expansion**	45	MTD from Part 1 or lower dose at the discretion of the investigator

*In any cohort the sponsor may elect to increase the sample size to up to 6 additional subjects.
**The expansion Phase may be reduced in the number of subjects for any reason.

3.4.3 DLT Definition (Part 1)

A DLT Event is defined as any of the following events assessed by the Investigator in accordance with the current version of CTCAE as probably or possibly related to AL3818 that occurs during or after the initial dose in Part 1 of this study on Day 8 through completion of the first multiple-dose course of therapy on Day 21, which cause any of the following:

1. CTCAE Grade 4 event

Hematologic Toxicity:
- Study-related febrile neutropenia (< 1.000 neutrophils/mm^3).
- Grade 4 neutropenia lasting > 7 days.
- Grade 3 hematologic toxicity with duration > 7 days.
- Study treatment-related Grade 4 thrombocytopenia or bleeding associated with Grade 3 thrombocytopenia.

Non-Hematologic Toxicity:
- Study treatment-related Grade 3 or 4 non-hematologic toxicity (excluding hyspersensitivity reaction to paclitaxel and/or carboplatin, constipation, electrolyte imbalance [hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemial, dehydration, anorexia, fatigue, nausea/vomiting lasting $\leq$ 48 hours with medical management] -including Grate 3 hypertension that continues more than 72 hours despite optimal medical management (Note: The prophylactic use of antihypertensive agents for Grade 1 and Grade 2 hypertension in order to minimize the occurrence of more severe or persistent hypertension while undergoing treatment with AL3818 does not constitute a Grade 3 toxicity).
- Any drug-related death.

If a DLT is experienced in any cohort, the cohort will be expanded to 6 subjects and the dose of AL3818 will be lowered to 10 mg. If at 10 mg a DLT is experienced, the dose of AL3818 will be lowered to 8 mg and so on for each DLT experienced. If two (2) DLTs are experienced in any cohort, the study will be paused until the safety events are evaluated. The maximum tolerated dose (MTD) will be defined as the dose level below that where 2 DLTs are experienced.

Guidelines for Hematologic Toxicity:
- Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).
- Subsequent courses of treatment (Cycles 2-6, Day 1) will not begin until:
    - ANC is $\geq$ 1,000 cells/mm^3, and
    - Platelet count is $\geq$ 100,000/mm^3
- Treatment will be delayed for a maximum of two weeks until these values are achieved.
- Patients who fail to recover adequate counts within a two-week delay will no longer receive protocol-directed therapy.

Modifications for Hematologic Toxicity:
Initial occurrence of dose-limiting neutropenia or dose limiting thrombocytopenia will be handled according to Table 3.4-2

Table 3.4-2: Dose Modifications for Dose-Limiting Hematologic Toxicity

AN	PL	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Reduce carboplatin one AUC unit (AUC	Add filgrastim or PEG-filgrastrim	Discontinue Protocol-Directed Therapy
Yes	Yes	Reduce AL3818 one dose level	Reduce carboplatin one AUC unit (AUC 4) *AND* add filgrastim or PEG-filgrastim	Discontinue Protocol-Directed Therapy
No	Yes	Reduce AL3818 one dose level	Reduce carboplatin one AUC unit (AUC 4)	Discontinue Protocol-Directed Therapy

Table 3.4-3: Modifications for Delayed Hematologic Recovery:
- Delay on the basis of neutropenia (Delay-ANC) is defined if the ANC is less than 1,000 cells/mm^3 within 24 hours prior to Day 1 of each cycle of scheduled therapy.
- Delay on the basis of thrombocytopenia (Delay-PLT) is defined if the platelet count is less than 100,000/ mm^3 within 24 hours prior to Day 1 of each cycle of scheduled therapy.
- Modifications noted below in Table 3.4-3 are only required for management of delays in the absence of dose reductions stipulated by nadir DLT-ANC and/or DLT-PLT.   In other words, if the patient experiences DLT-ANC and Delay-ANC, make the modifications as indicated for the nadir counts without additional modifications based on delayed recovery. AL3818 is continued despite treatment delays in the absence of a DLT.

Table 3.4-3. Modifications for delayed Hematologic Recovery

Category	Delay (days)	Modification
Delay-ANC	1-7	No Change
	8-14	Follow Table 3.4-2 for dose modifications with next cycle
	>14	Discontinue Protocol-Directed Therapy
Delay-PLT	1-7	No Change
	8-14	Follow Table 3.4-2 for dose modifications with next cycle
	>14	Discontinue Protocol-Directed Therapy

Table 3.4-4: Chemotherapy Dose Levels

Drug	Regimen -2 Level	Regimen -1 Level	Regimen Starting Dose
Paclitaxel Regimen 1	110 mg/m^2 Day 1	135 mg/m^2 Day 1	175 mg/m^2 Day 1
Carboplatin	-	4	5

Neuropathy:
- Peripheral Neuropathy Grade 2 (or greater) requires reduction of one dose level in paclitaxel and delay in all subsequent protocol-directed therapy for a maximum of three weeks until recovered to Grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due, the patient will no longer receive protocol-directed therapy and will come off the study. If Grade 2 (or greater) neuropathy recurs after 2 dose reductions of paclitaxel, the patient will no longer receive protocol-directed therapy and will come off the study.

Renal Toxicity:
- Renal toxicity (associated with reduction in GFR) is not expected from carboplatin as a direct complication of chemotherapy in this patient population using the prescribed dose and schedule of each regimen. As such, there are no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any patient who develops renal insufficiency, defined by serum creatinine greater than 1.5 x institutional upper limit normal (ULN), CTCAE Grade $\geq$ 2 (see Appendix B).

Hepatic Toxicity:
- Hepatic toxicity is not expected as a direct complication of chemotherapy in this patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of two weeks until recovered to $\leq$ Grade 1. If Grade 3 (or greater) elevations recur, the patient will be removed from the study.

There will be no dose modifications for alopecia, constipation, hypokalemia, hypocalcemia, hypomagnesemia, or hypophosphatemia. It is recommended that routine medical measures be employed to manage constipation, and electrolyte abnormalities.

In general, the occurrence of a hypersensitivity reaction to paclitaxel, carboplatin is not considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made. However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the patient will no longer receive that agent. Patients removed from study for hypersensitivity reactions will be replaced if they have completed < 1 cycles of therapy and have not experienced a DLT.

Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require discussion with the study chair or co-chair except where noted below.

Special Modifications Study Treatment:

For any CTCAE Grade 3 non-hematologic adverse event (except controllable nausea/vomiting, constipation, diarrhea, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, or dehydration) considered to be at least possibly related to study treatment, protocol directed treatment should be held until symptoms resolve to ≤ CTCAE Grade 1. If a CTCAE Grade 3 adverse event persists for > two weeks or recurs after resumption of therapy, the patient may be taken off protocol directed treatment after consulting with the Study Chair.

For any CTCAE Grade 4 non-hematologic adverse events (except controllable nausea/vomiting, constipation, diarrhea, hypokalemia, hypocalcemia, hypomagnesemia, or hypophosphatemia), the patient may be taken off protocol directed treatment therapy after consulting with the Study Chair.

For all ≥ Grade 3 hematological or non-hematological AEs that are NOT AL3818 related:

After consultation with the PI and at the discretion of the treating physician, AL3818 dosing may be maintained provided that the patient can continue to take the agent by mouth, or via other enteral route.

3.4.4   Part 2 Stopping Rule

In Part 2, the Medical Monitor will stop study enrollment to evaluate safety if a subject experiences a related DLT event as defined in Section 3.4.3 that does not resolve with a dose reduction, or which occurs in multiple subjects. The Medical Monitor will also consider stopping the study if there are multiple related SAEs that are of similar origin.

If the study is temporarily stopped by the Medical Monitor for a further safety evaluation, subjects that are stable and ongoing may continue on therapy. No new subjects may be enrolled until the evaluation is complete. The study may be reinitiate enrollment if the Medical Monitor and Investigators determine that the concerning events are manageable and/or not related to study medication.

3.4.5   Dose Modifications

If at any time during treatment with AL3818 a subject experiences significant and intolerable side effects, a dose reduction may be implemented according to the following guidelines.

3.4.5.1   Dose Reductions for Toxicity

Dose reductions may be implemented at the discretion of the investigator if the patient experiences significant non-DLT related toxicities during treatment as described in Table 3.4-5 shown below. Once a patient's dose has been reduced, it should not be escalated to the previous dose level. For the dose escalation phase of the study the following table should be used as a guide for dose reductions. Once an MTD is established in Part 1 of the study, dose reductions will be at the discretion of the investigator. Dose Modifications based on Grade (excluding hypertension) can be found in Table 3.4-6.

Table 3.4-5: AL3818 Dose Reductions for Toxicity

Dose Level	Cohort 1
0 (starting dose)	12 mg
-1 (first reduction)	10 mg
-2 (second reduction)	8 mg
-3 (third reduction)	Discontinue

Table 3.4-6: AL3818 Dose Modification Based on Grade**

Grade of Event	Management / Next Dose
≤ Grade 1	Symptomatic care No change in Trial Drug dose
Grade 2	Treat symptomatically. If adverse event does not resolve within 48 hours to ≤ Grade 1 then **Hold Trial Drug** until recovery to ≤ Grade 1 and resume Trial Drug at the same dose. If adverse reaction recurs consider dose reduction at the discretion of the investigator.
Grade 3	Treat symptomatically. If adverse event does not resolve to Grade 2 or below within 48 hours with maximal supportive care then **Hold Trial Drug**[1] until ≤ Grade 1 or up to 14 days then resume Trial Drug at one dose level lower[2]. If Grade 3 event persists or recurs then discuss with Lead Investigator before recommencing Trial Drug.
Grade 4	**Discontinue Trial Drug permanently**

**Does not include hypertension
1.   Patients requiring a delay > 14 days should stop Trial Drug.
2.   Patients requiring > 1 dose reduction should stop Trial Drug.

Dose Modification for increases in AST/ALT, bilirubin and amylase can be found below in Table 3.4-7.

Table 3.4-7: AL3818 Dose Modifications for increased ALT/AST, Bilirubin and Amylase Levels

Event	AL3818 Dose Modification*
ALT or AST less than or equal to Grade 1 with bilirubin less than or equal to Grade 1	No dose reduction
ALT and/or AST of greater than or equal to Grade 2 with bilirubin greater than or equal to Grade 2 or ALT and/or AST greater than or equal to Grade 3	Withhold and resume upon recovery 1st episode----1 Level dose reduction 2nd episode----2 Level dose reduction 3rd episode----Discontinue from Study
Amylase less than or equal to Grade 1	No dose reduction 1st episode----1 Level dose reduction 2nd episode----2 Level dose reduction 3rd episode----Discontinue from Study
Amylase of greater than or equal to Grade 2	Withhold and resume upon recovery
All other Non-Hematologic AE greater than or equal to Grade 3	Withhold and resume upon recovery 1st episode--1 Level dose reduction 2nd episode----2 Level dose reduction 3rd episode----Discontinue from Study

* See Table 3.4-5 for dose level reductions

Dose modification and antihypertensive therapy for hypertension can be found in Table 3.4-8 accompanied by a table for antihypertensive medications by class (Table 3.4-9)

Table 3.4-8: AL3818 Dose Modification and Therapy for Hypertension.

Grade (CTCAE v.4.0)	Antihypertensive Therapy	Blood Pressure Monitoring	AL3818 Dose Modification
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-89		Standard	No Change
Persistent Grade 2- Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v.4.0	Step 1) Initiate BP treatment and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another anti-hypertensive Rx, a LA DHP CCB, ACE1, ARB, or ABB; increase dose of this drug as described in step 1 Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of AL3818 or stopping AL3818 *NOTE: Stopping or reducing the dose of AL3818 is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician	No change except as described in step 4
Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including the CTCAE v.4.0.	HOLD AL3818 until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see steps 1-4 above) **with 2 major exceptions: 1) If systolic BP >180 or diastolic BP >110 and the patient is symptomatic: optimal management with intensive IV support in ICU; STOP AL3818 and notify hospital staff that stopping AL3818 may result in a decrease in BP and2) If systolic BP >180 or diastolic BP >110 and the patient is asymptomatic,**	BP should be monitored as recommended by the treating physician **unless the patient is symptomatic with systolic BP >180 or diastolic BP >110 in which case,**	HOLD AL3818 until systolic BP ≤159 and diastolic BP ≤99. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive

	2 new antihypertensives must be given together in step 1(and dose escalated appropriately as in step1). *NOTE:* Stopping or reducing the dose of AL3818 is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose ofantihypertensive medication(s)accordingly	**Monitoring should be intensive.**	medications, consider either 1 dose reduction of AL3818 or stopping AL3818. **HOWEVER, If the patient requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue AL3818 or if BP is controlled, re-start AL3818 at 1 lower dose level after consultation with the study Principal Investigator (PI)
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP AL3818 and notify hospital staff that stopping AL3818 may result in a decrease in BP**	Intensive	Permanently discontinue AL3818 or if BP is controlled, re-start AL3818 at 1 lower dose level after consultation with the study Principal Investigator

Abbreviations: Long acting (LA), Dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB), alpha beta blocker (ABB)

- *See table below for suggested antihypertensive medications by class
- If patients require a delay of >4 weeks for management of hypertension, discontinue protocol therapy
- If patients require >1 dose reductions, discontinue protocol therapy
- Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in AL3818
- 24-48 hours should elapse between modifications of antihypertensive therapy
- Hypertension should be graded using CTCAE v.4.0.

Table 3.4-9: Suggested Antihypertensive Medications by Class**

Agent Class	Agent	Initial Dose	Intermediate Dose	Maximum Dose	Hepatic Metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP3A4 substrate**
	amlodipine	**2.4 mg daily**	**5 mg daily**	**10 mg daily**	**CYP3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP2D6 substrate and inhibitor

**** Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug interactions with you through CYP450 in case this issue exists

While patients are receiving treatment with AL3818, the early initiation of antihypertensive treatment for grade 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 AE. Decisions to hold or decrease the dose of AL3818during treatment must be based on BP readings taken in the clinic by a medical professional.

Dose modification for Hand-Foot Syndrome can be found below in Table 3.4-10.

Table 3.4.10: Recommended PLD Dose Modification Guidelines for Hand-Foot Syndrome (HFS)

Toxicity Grade	Dose Adjustment
1: mild erythema, swelling, or desquamation not interfering with daily activities	Redose AL33818 at same dose level and initiate HFS skin care per institutional guidelines.
2: erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations <2 cm in diameter	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, AL8318 should be dose reduced one dose level. If resolved to Grade 0–1 within 2 weeks, continue treatment at previous dose. If patient experienced previous Grade 3–4 toxicity, continue treatment AL3818 with a dose reduction and obtain Dermatology consultation. Continue HFS skin care per institutional guidelines.
3: blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Decrease AL3818 dose by one dose level. Dermatology Referral. Continue HFS skin care per institutional guidelines. If after 2 weeks there is no resolution, AL3818 should be discontinued.
4: diffuse or local process causing infectious complications, or a bed ridden state or hospitalization	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Decrease AL3818 dose by one dose level. Obtain dermatology consult and continue HFS skin care per institutional guidelines**.** If after 2 weeks there is no resolution, AL3818 should be discontinued.

3.4.6　　　　　Dose Interruption

During the first 21 days of Part 1 of this study (i.e. completion of the first 21-day cycle of therapy), subjects should attempt to take all study medication. Subjects who do not take their medication for at least 12 of 14 days (> 80 % of scheduled doses) during this period will not be evaluable for safety and will be discontinued from the study (see Section 3.7).

After the first 21 days of Part 1 and in Part 2 of this study, AL3818 treatment may be temporarily stopped for up to 14 days due to scheduling, side effects or other factors whether related or unrelated to study drug. If resumed, the dose of AL3818for an individual subject may be maintained at the previous dose level or decreased as described above in Section 3.4.4 (i.e. downward dose adjustment at discretion of the investigator).

Dose interruptions are only allowed for non-DLT events. If an event defined as a related DLT in Part 1 of this study is observed during Part 2 or the extension period of Part 1 (after Day 21), the subject should be discontinued unless patient is experiencing benefit from the therapy. In this case, discussion with Medical Monitor is required prior to restarting patient at a lower dose.

Subjects who experience a related adverse drug reaction that results in a drug interruption and that does not return to baseline or ≤ Grade 1 within 14 days from drug interruption, should be removed from the study and not re-challenged.

3.5　　　　　Concomitant Medications

3.5.1　　　　Prior and Concomitant Medications

Prior medications are defined as medications that were taken within 30 days prior to initial dosing with study drug.

Concomitant medications are defined as medications taken any time after the start of dosing until the final visit at 4 to 5 weeks after the last dose of study drug.

During the clinical trial, standard supportive care for the underlying malignancy including antihypertensive, antibiotics, antifungals, and antiemetics medications may be administered according to standard medical practice. All concomitant medications including prophylactic antibiotic therapy, antiemetics, and stimulating factors of blood components (granulocyte-colony stimulating factors, platelet stimulators), or transfusions will be recorded on the concomitant medication page of the case report form (CRF).

3.5.2　　　　Prohibited Concomitant Medications

Concomitant administration of any other anti-neoplastic therapy is prohibited. Treatment with any strong inhibitors or inducers of CYP3A4, CYP2C9 and CYP2C19 should also be avoided while on AL3818 treatment. It is also recommended that any foods, such as grapefruit juice, that are known to be strong inhibitors or inducers of CYP3A4, CYP2C9 or CYP2C19 are avoided

during this trial. If any prohibited medications are administered, the Sponsor's Medical Monitor must be contacted immediately for discussion as to whether the subject will be discontinued from receiving further AL3818.

3.6   Duration of Therapy

In the absence of CTCAE Grade 3 or 4 toxicity, study drug may be administered per protocol for the 21-day continuous course therapy for up to 18 months or until one of the following criteria applies, whichever occurs first:

- Disease progression

- Intercurrent illness that may interfere with safe administration of study drug (as determined by the Investigator)

- One or more adverse events that, in the opinion of the Investigator and in consultation with the Sponsor or the Sponsor's designee, poses an unacceptable risk

- An adverse drug reaction that is defined in the protocol as a significant side effect (grade 3 or better) requiring a dose interruption, that does not resolve (Baseline or $\leq$ Grade 1) after a dose reduction or dose interruption for up to 14 days

- Subject decides to withdraw from the study

- Sponsor decides to halt the study

3.7   Procedures for Monitoring Subject Compliance

Subjects will return to the clinic for safety evaluations and drug supply according to the schedule in Appendix A.

For subjects in Part 1 of this study, if more than two consecutive doses of study drug are missed, continued participation in the study will be decided on a case-by-case basis by the Investigator in consultation with the Medical Monitor and Sponsor.   To be considered evaluable for safety in Part 1 of this study, subjects must take at least 12 of 14 days (> 80 %) of their scheduled medication in the first continuous dosing cycle (through Day 21). Subjects who do not take at least 12 days of their scheduled medication for the safety evaluation portion of Part 1 will be replaced to ensure that a complete evaluable cohort is obtained.

4.0   STUDY POPULATION

The study population will be female subjects 18 years of age or older who have the following cancers:
- Recurrent or metastatic endometrial cancer subjects with tumors of all histologies

- Recurrent or metastatic ovarian cancer subjects

- Recurrent or metastatic cervical cancer subjects

requiring treatment with further platinum-based chemotherapy $\geq$ 6 months after their last cycle of first- line chemotherapy and 6 weeks after maintenance that is not chemotherapy based.

4.1   Inclusion Criteria

For a subject to be eligible for this study, she must meet all of the following criteria:

1. Female subjects 18 years of age or older

2. Subjects may be enrolled with previous histologically proven diagnosis of following:

   a.   Endometrial Cancer: Patients must have recurrent or persistent endometrial carcinoma, which is refractory to curative therapy or established treatments. Histologic diagnosis will be reviewed by the treating institution. Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified, mucinous adenocarcinoma, squamous cell carcinoma, and transitional cell carcinoma.

   Initial treatment may have included chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy; antiangiogenic therapy (e.g. bevacizumab) as part of adjuvant therapy is allowed. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer was counted as a systemic chemotherapy regimen.

   Patients are not allowed to have received additional cytotoxic or non-cytotoxic therapy for management of recurrent or persistent disease. Endometrial patients must be chemotherapy naïve or could have had adjuvant radiation therapy.

   b. Ovarian cancer: Patients must have recurrent or persistent ovarian or primary peritoneal cancer, which is refractory to established treatments.

   Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified.

   Patients must have received one prior platinum-based chemotherapeutic regimen for the management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial therapy may have included high-dose therapy, consolidation, or extended therapy adminitstered after surgical or non-

surgical assessment. Antiangiogenic therapy (e.g. bevacizumab) as part of adjuvant therapy is allowed.

Patients are not allowed to have received additional cytotoxic or non-cytotoxic therapy for management of recurrent or persistent disease. Patients must have disease which is refractory to conventional platinum therapy and has relapsed within 6 months of completion of primary platinum-based treatment.
Patients could be chemotherapy naïve or could have had one prior platinum-based regimen and would receive AL3818 combined with carboplatin and taxol in the 2nd line setting for platinum-sensitive recurrent disease.

   c. Cervix cancer: Subjects diagnosed with histologically confirmed squamous cell carcinoma of the cervix, which are resistant to conventional platinum therapy and have relapsed within 6 months of treatment. Patients with the following histologic epithelial cell types are eligible: squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma.

requiring treatment, after one prior line of therapy, with further platinum-based chemotherapy $\geq$ 6 months after their last cycle of first-line chemotherapy and 6 weeks after maintenance that is not chemotherapy based.

3. All patients must have measurable disease. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be $\geq$ 20mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or $\geq$ 10mm when measured by spiral CT.

4. Life expectancy $\geq$ 3 months

5. Subject must be suitable for oral administration of study medication

6. Patients must have signed an approved informed consent and authorization permitting release of personal health information.

7. Patient must have adequate:
   a. Bone Marrow Function: Absolute neutrophil count (ANC) greater tgen of equal to 1,500/mm^3, equivalent to Common Toxicity Criteria (CTC) grade 1. Platelets greater than or equal to 100,000/mm^3
   b. Renal Fucntion:: Creatinine less than or equal to 1.5 x institutional upper limit normal (ULN), CTC grade 1. Note: If creatinine is greater than 1.5 x ULN, creatinine clearance must be greater than >50 mL/min.
   c. Hepatic Fucntion: Bilirubin less than or equal to 1.5 x ULN (CTC grade 1) or less than or equal to 3.0 x ULN for subjects with Gilbert Syndrome; AST and ALT less than or equal to 3.0 ×ULN.
   d. Coagulation profile: PT such that international normalized ratio (INR) is $\leq$ 1.55 (or an

in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin or low molecular weight heparin) and a PTT < 1.2 times control.

8. ECOG performance status ≤ 2

9. Subjects of child-bearing potential must agree to use contraceptive measures starting 1 week before the administration of the first dose of AL3818 until 4 weeks after discontinuing study drug

10. Subjects of child-bearing potential must have a negative serum pregnancy test prior to study entry and cannot be lactating. ,.

11. Ability and willingness to comply with the study protocol for the duration of the study and with follow-up procedures

4.2   Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Subjects who have received prior treatment with an FGFr inhibitor or antagonist of FGFr.

2. Patients who have received prior antiangiogenic therapy, including bevacizumab, sorafenib, sunitinib.

3. Patients with serious, non-healing wound, ulcer or bone fracture.

4. Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.

5. Patient with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases or history of cerebrovascular accident (CVA, stroke) transient ischemic attack (TIA) or subarachnoid hemorrhage within 6 months of the first date of treatment on this study.

6. However, patients with metastatic CNS tumors may participate in this trial, if the patient is > 4 weeks from therapy completion (including radiation and/or surgery), is clinically stable at the time of study entry and is not receiving corticosteroid therapy.

7. Patients with proteinuria. Patients discovered to have a urine protein of 1+ on dipstick or ≥ 30 mg/dl at baseline should undergo a 24-hour urine collection, which must be an adequate collection and must demonstrate < 1000 mg protein/24 hours to allow participation in the study.

8. Patients with clinically significant cardiovascular disease; this includes: Uncontrolled hypertension; Myocardial infarction or unstable angina within 6 months prior to

registration; New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix F); Serious cardiac arrhythmia requiring medication; Grade II or greater peripheral vascular disease (Appendix F)

9. Patients who are pregnant or nursing. To date, no fetal studies of AL3818 in animals or humans have been performed. Therefore, AL3818 should not be administered to pregnant women. Subjects will be apprised of the large potential risk to a developing fetus. It is not known whether AL3818 is excreted in human milk. Because many drugs are excreted in human milk, AL3818 should not be administered to nursing women. Women of childbearing potential must agree to use contraceptive measures during study therapy and for at least 3 months after completion of AL3818 therapy.

10. Patients with uncontrolled hypokalemia, hypomagnesaemia, and/or hypocalcaemia.

11. Hemoptysis within 3 months prior to first scheduled dose of AL3818.

12. Patients with acute or chronic liver disease, active hepatitis A or B with known cirrhosis or liver dysfunction.

13. Cytotoxic chemotherapy, immunotherapy, or radiotherapy within 4 weeks (6 weeks in cases of mitomycin C, nitrosourea, lomustine) prior to first scheduled dose of AL3818 or a major surgical procedure within 28 days or minor surgical procedure performed within 7 days prior to first scheduled dose of AL3818.

14. Concomitant treatment with strong inhibitors or inducers of CYP3A4, CYP2C9 and CYP2C19 who cannot be switched to other alternative medications (See Appendix E).

15. Known history of human immunodeficiency virus infection (HIV).

16. Subjects with active bacterial infections (other than uncomplicated urinary tract infection) and/or receiving systemic antibiotics.

17. Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of other cancer present within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy.

18. History of non-malignant GI bleeding, gastric stress ulcerations, or peptic ulcer disease within the past 3-months that in the opinion of the investigator may place the patient at risk of side effects on an anti-angiogenesis product.

19. History of significant vascular disease (e.g. aortic aneurysm, aortic dissection).

20. Intra-abdominal abscess within the last 3 months.

21. History of uncontrolled hypertension that is not well managed by medication, as

documented by 2 baseline evaluations taken one hour apart with systolic blood pressure >160 mm or diastolic blood pressure >90 mm Hg pressure, or that in the opinion of the investigator may place the patient at risk when taking a VEGF inhibitor.

22. Pre-existing uncontrolled hypertension as documented by 2 baseline BP readings taken at least one hour apart, defined as systolic bloodpressure (BP) >160 mm Hg or diastolic BP > 90 mm Hg pressure.

23. QTcF>470 msec on screening ECG.

24. A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).

25. The use of concomitant medications that prolong the QT/QTc interval.

26. Baseline echocardiogram (within 2 months) with left ventricular ejection fraction (LVEF) < 50%.

27. History of difficulty swallowing, malabsorption, active partial or complete bowel obstruction, or other chronic gastrointestinal disease or condition that may hamper compliance and/or absorption of AL3818.

28. History of pancreatitis and/or renal disease or pancreatitis that includes histologically confirmed glomerulonephritis, biopsy proven tubulointerstitial nephritis, crystal nephropathy, or other renal insufficiencies.

29. Treatment with an investigational agent within the longest time frame of either 5 half-lives or 30 days of initiating study drug.

30. Known recreational substance abuse.

31. Known hypersensitivity to AL3818 or components of the formulation.

5.0   SAFETY ASSESSMENTS

5.1   Collection of Adverse Events Data

Data regarding treatment-emergent AEs will be collected in this study. Treatment-emergent AEs are events that are not present at baseline, or if present at baseline, have worsened in severity. AEs will be assessed at each study visit from the time of study drug administration on Study Day 1 through the final visit occurred at 4 to 5 weeks following the last dose of study drug. AEs assessed by the Investigator as related to study drug and "ongoing" at the final scheduled study visit will be monitored by the Investigator until resolved or stabilized.

Each subject will be observed and queried by the Investigator or his/her designee at each study visit for any continuing AEs or new AEs since the previous visit. If an AE occurs between study visits, regardless of causal relationship to study drug and in the opinion of the Investigator, requires a study visit for full evaluation, the subject will be asked to return to the CRU for an unscheduled visit.

Any AE reported by the subject or noted by the Investigator or his/her designee will be recorded on the CRF. The following information will be recorded for each AE: description of the event, date and time of onset, date and time of resolution, severity, causal relationship to study drug, outcome, action taken with the study drug and any treatment given.

All abnormal changes from baseline in physical examination findings, vital signs, ECGs, and laboratory evaluations will be collected, graded with regards to severity or clinical significance, assessed for causal relationship and will be recorded on the CRF.

5.2   Clinical Laboratory Evaluations

During Part 1 of the study blood samples will be collected for laboratory evaluation. Blood samples will be collected at screening/baseline (Day -14 to 1 prior to dosing), and on Days 1, 8, 15, 22, 29, 43, 64, 85 and 106. Urine specimens will be collected at screening for baseline.

In Part 2 of the study blood samples for laboratory evaluation will be collected at screening/baseline (Day -14 to 1 prior to dosing), and on Days 1, 8, 22, 29, 43, 64, 85, 106 and 127. Urine specimens will only be evaluated at screening for baseline.

Evaluations in extension periods will be according to Appendix A3.

If a clinically significant laboratory value is obtained on the last day of dosing in the study, then the laboratory evaluation will be repeated at the final visit.

Baseline blood and urine samples must be collected within 72 hours (Day -14 to Day 1) prior to administration of the study drug on Day 8. Results must be evaluated prior to dosing. If an abnormal test result of clinical significance is obtained at baseline that was not clinically significant at screening, the test may be repeated within 24 hours and dosing will be delayed

until the value is no longer clinically significant.

Subjects with clinically significant abnormal laboratory values during the study will be monitored until the value is no longer considered clinically significant or no further change is anticipated. All abnormal changes from baseline in laboratory values will be collected, graded with regards to severity, assessed with regards to causality and recorded in the CRF to be reported as abnormal laboratory findings. Only clinically significant abnormal laboratory findings associated with clinical sequelae or that requires therapeutic intervention are considered AEs. All clinical laboratory analyses will be performed at the clinical site and the results will be recorded on the appropriate CRF. Clinical laboratory reports must be reviewed, signed, and dated by the Investigator. The Investigator for clinical significance will assess each abnormal test result and the result of the evaluation will be recorded on the CRF.

5.2.1 Hematology

Complete blood cell count (CBC) with differential.

5.2.2 Serum Chemistry

Comprehensive metabolic panel will include serum alkaline phosphatase, ALT, AST, glucose, calcium, phosphorus, chloride, sodium, potassium, BUN, creatinine, total bilirubin, albumin, total protein, amylase, bicarbonate/carbon dioxide (CO_2), uric acid, and lactate dehydrogenase (LDH). TSH, T3, and T4 will be measured at baseline and on Day 22, 43 and 64 in Part 1. In Part 2 measurements will be at baseline and Day 22, 43, and 64. Evaluations in extension periods will be according to Appendix A3.

5.2.3 Triglycerides

Samples will be taken for evaluation of triglycerides (amylase and lipase).

5.2.4 Urinalysis

Urinalysis will be done only at screening for subject enrollment and may include appearance, color, pH, specific gravity, glucose, protein, ketones, blood, creatinine clearance, and a detailed microscopic analysis. Microscopic analysis will be performed regardless of macroscopic results and will include the following: WBC, RBC, cast/type, crystal/type, and bacteria. Standard urinalysis will be conducted on the same days as blood chemistry. Evaluations in extension periods will be according to Appendix A3.

5.2.5 Lipid Profile, Amylase and Lipase

Blood samples will be taken to evaluate a full lipid profile as well as amylase and lipase levels to monitor for acute pancreatitis. In Part 1 of this study blood samples for a full lipid profile will be collected at screening/baseline (within 14 days prior to initial dosing), and on Days 22, 43 and 64. In Part 2 of this study, blood samples for a full lipid profile will be collected at screening/baseline (within 14 days prior to initial dosing), and on Days 1, 22, 43 and 64, as well

as any Follow-up visit or Final Study Visit. During the continuation period, a full lipid profile is conducted at the end of each three cycles of treatment (Day 64) and at the Final Study Visit.

5.2.6   Thyroid Function Test

Thyroid function testing (TFT) will include thyroid hormones such as thyroid-stimulating hormone (TSH, thyrotropin), thyroxine (T4), and triiodothyronine (T3). In Part 1 of this study blood samples for TFT will be collected at screening/baseline (within 14 days prior to initial dosing) and on Days 22, 43 and 64. In Part 2 of this study, blood samples for TFT will be collected at screening/baseline (within 14 days prior to initial dosing) and on Days 22, 43 and 64, as well as any Follow-up visit or Final Study Visit. During the continuation period, TFT is conducted at the end of each three cycles of treatment (Day 64) and at the Final Study Visit.

5.2.7   Coagulation Profile

Coagulation tests will include aPTT, INR, haptoglobin and fibrin degradation products (FDPs). In Part 1 of this study blood samples for coagulation tests will be collected at screening/baseline (within 14 days prior to initial dosing) and on Days 1, 15 and 64. The baseline blood samples must be collected far enough in advance to allow for evaluation of results prior to dosing on Day 1. If a clinically significant laboratory value is obtained on the last day of dosing in the study, then the laboratory evaluation will be repeated every two weeks or at the discretion of the investigator and at the final visit 4 to 5 weeks after discontinuation of therapy.

In Part 2 of this study, blood samples for coagulation tests will be collected at screening/baseline (Within 14 days prior to initial dosing) and on Days 1, 8, 22 and 64. Evaluations in extension periods will be according to Appendix A3.

5.3   Physical Examinations and Medical History

5.3.1   Complete Physical Examination

The Investigator or designee will perform a complete physical examination at screening. Results will be recorded on the appropriate page of the CRF. Assessments of height, weight, calculation of body surface area (BSA), and vital signs will be recorded on the CRF.

5.3.2   Medical History

A medical history will be obtained at screening. Medical history will include demographic data (age, gender, race/ethnicity, etc.). In addition to general medical conditions, specific information relative to the malignancy will be obtained and recorded in the CRF:

• Date of initial diagnosis, staging, and date of disease progression or recurrent disease

• Date and duration of previous cancer therapies including radiotherapy, chemotherapy, and immunotherapy

• Date of surgical interventions for treatment of the malignancy, if any

5.4   Vital Signs

Systolic and diastolic blood pressure, radial pulse, respiratory rate and temperature will be obtained with the subject in a sitting position at rest for at least 5 minutes during each visit and physical examination.

5.5   ECG

Part 1: A standard supine (after resting for at least 5 minutes) 12-lead ECG will be performed once by a trained technician at screening and baseline (within -14 to 1 days prior to receiving dose 1 of study drug on Day 8), one time on Days 8 (between 3 and 5 hours post-dose), Day 15 and after Day 22 of dosing in Part 1 (pre-dose and post-dose), and at the final visit.

Part 2: A standard supine (after resting for at least 5 minutes) 12-lead ECG will be performed once by a trained technician at screening and baseline (within -14 to 1 days prior to receiving dose 1 of study drug on Day 8), at the end of each three cycles of therapy (Day 64), and at the final visit.

A single ECG is obtained.

Baseline ECGs will be performed. The ECG report must be reviewed, signed, and dated by the investigator or cardiologist. One duplicate copy of the ECG tracing and the evaluation report will be printed and sent to the Sponsor after de-identifying the subject for inclusion with the CRF. The original ECG results will be kept on file at the site as source documentation.

5.6   Weight

Body weight will be measured in kilograms at screening and baseline. The baseline value will be used to calculate BSA for determining the initial dose of AL3818 (see Section 9.2). Weight change will be evaluated between the baseline, at each visit and end of each 21-Day cycle visit. Weight will also be measured at the final visit at 4 to 5 weeks after the last AL3818 dose or at the end of cycle visit if the subject is enrolled in the extension period.

5.7   Pregnancy Test

A serum (ß-hCG) pregnancy test will be administered to females of childbearing potential at screening. The investigator may also conduct additional optional pregnancy tests as appropriate to confirm that the patient is not pregnant at the time of enrollment. If a serum ß-hCG pregnancy test is suspected to be a false positive, the absence of pregnancy can be confirmed by a gynecologic examination.

If a pregnancy occurs in the subject or in the partner of a subject during the course of the study, the Investigator must report it to the Sponsor within 24 hours as a serious adverse event. For females who experience pregnancy during the trial, the study medication will be discontinued

immediately and patient monitored for any adverse problems with the pregnancy.

5.8   Echocardiogram

A routine echocardiogram with left ventricular ejection fraction (LVEF) assessment will be conducted at screening (within 2 months prior to dosing on Day 8). If a routine echocardiogram was conducted within 2-months (even if prior to consent of the patient), these results may be used for study admission. LVEF must be at least 50 % for the subject to qualify for the study.

5.9   Imaging Studies

Tumor and CNS imaging to exclude subjects with CNS metastases, if deemed necessary by the investigator, must be performed within 21 days prior to dosing on Day 8. In addition, imaging scans appropriate to the location of the tumor are to be performed at the end of every two 21-Day cycle of therapy (see Section 8.0) for both parts of the primary study and the extension period and at the Follow-up visit.

5.10   Documentation of Concomitant Medications

Details regarding the name, indication, dose, route of administration, and frequency of all prescription medications, over-the-counter medications, or alternative therapies taken within 30 days prior to the first dose of study drug through 21 days after the last dose of study drug will be recorded on the CRF. Any additions, deletions, or changes in the dose of these medications during the trial will be recorded on the CRF. (See Section 3.5 for more information regarding concomitant medications.)

6.0   PHARMACOKINETICS

No PK assessments will be performed in study.

7.0   PHARMACODYNAMICS

If desired, tumor marker FGFR2 will be measured at baseline (within 7 days prior to receiving the first dose) and at the end of Part 1 (Day 127) and in Part 2 or during long term continuation of treatment each six 21-Day cycles of therapy, and at the final visit.

8.0   EFFICACY

Tumor evaluations will be performed using an appropriate imaging technique at screening/baseline (day -14 to -1), at the end of Part 1, and every three 21-Day cycles (127-days) of treatment. Tumor evaluations will include imaging scans by an appropriate technique for determination of response assessed by RECIST 1.1 (see Appendix D). The same method used to document measurable and evaluable disease at baseline should be used consistently for all evaluations throughout the study in a given subject.

ECOG Performance Assessment will be performed at screening/baseline (Day -14 to 1), Day

22 and Day 64 in Part 1 and every six 21-Day cycles in Part 2 or patients from Part 1 in the extension phase, and at the final visit. An exposure-response analysis will be performed to assess the dose response in this study.

9.0   STUDY VISITS

Refer to Appendix A for the Schedule of Study Procedures.

9.1   Screening

The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the Informed Consent Form. Written informed consent must be provided by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. The signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

After written informed consent is obtained, the subject will be assigned an eight-digit screening number and will undergo the designated screening procedures listed in Appendix A within 14 days prior to study drug administration. The Investigator will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in Section 4.0.

Screening assessments are assessment of medical history, concomitant medications, physical examination, vital signs, weight, serum ß-hCG or other pregnancy testing, and laboratory evaluations (CBC, CMP, urinalysis, coagulation profile, and lipid profile), Echocardiogram, ECG, ECOG Score, and MRI or Spiral- CT (within 21 days). Baseline tumor values for PD endpoints (tumor markers) will be obtained within 21 days prior to dosing on Day 8. Each subject who meets screening and baseline criteria will be assigned a treatment number.

9.2   Baseline Evaluations

Following the screening visit, subjects determined to be eligible for participation in the study will undergo baseline assessments. Baseline assessments are assessment of concomitant medications, vital signs, weight, serum ß-hCG or other pregnancy testing, and laboratory evaluations (CBC, CMP, urinalysis, coagulation profile, and lipid profile), ECG and baseline measurements of serum antibody to AL3818. Baseline tumor values for PD endpoints (tumor markers) will be obtained within 21 days prior to dosing on Day 8. Each subject who meets screening and baseline criteria will be assigned a treatment number. Subjects will be assigned to a cohort based on the order of entry into the study.

9.3   Single-Dose Period (Study Part 1 Only)

Following completion of screening and baseline assessments on Day -14 to -1, subjects will

receive an initial oral dose of AL3818 on Day 8 in the CRU. Subjects will remain at the CRU for approximately 8 hours following dosing for observation and performance of post-dosing safety evaluations. Subjects will be discharged after the 8 hour post-dose observation period, unless in the opinion of the investigator safety considerations warrant an extended in-subject observation. The site may also retain a patient longer than 8 hours if deemed necessary to complete all study related procedures. Subjects will return to the CRU for safety and efficacy assessments per the schedule for their cohort in Appendix A.

9.4   Multiple-Dosing Period

During the multiple dosing periods (Day 1-127) in Part 2 and as maintenance therapy for 18 months in Part 2 or for continuation subjects in Part 1, consecutive daily dosing will be conducted as indicated in Appendix A3 with six 21-Day cycles of 7 days rest and 14 days active treatment combined with chemotherapy which is administered on Day 1 of each cycle. During this time, safety preliminary efficacy, and other assessments will be performed as indicated in Appendix A2 (Part 2 subjects) or A3 (continuation subjects).

9.5   Follow-Up Visits

A follow-up visit will be conducted 21 days after the last dose of AL3818 for safety and efficacy evaluations as described in the Appendix A tables. If a subject continues use of study medication for repeat 21-Day cycle(s), the subject will return for safety and efficacy evaluations as described in Appendix A3. After discontinuation of therapy for any reason, at 4 to 5 weeks after the last dose of AL3818 subjects will return for the final study visit. At this visit, safety, pharmacodynamics, efficacy, and other assessments will be performed as described in

Appendix A2 or A3.

10.0   PREMATURE DISCONTINUATION FROM STUDY

A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria before receiving first dose of study drug has been administered
- Death
- Lost to follow-up after every attempt has been made to contact the subject including sending a registered letter
- Subject withdraws consent

Subjects in Part 1 of this study should complete the Day 21 assessment and compliance to medication should confirm that at least 12 of 14 days ($> 80\%$) of the scheduled doses were taken on schedule. If subjects fail to take at least 12 days of the scheduled doses, they should be

replaced in that cohort for purposes of evaluating safety and dose escalation.

The Principal Investigator and the Institutional Review Board/Ethics Committee (IRB/EC) reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative reasons.

11.0   PREMATURE DISCONTINUATION FROM STUDY DRUG

Subjects discontinuing from the study drug prematurely will be encouraged to return for scheduled follow-up evaluations, including the final study visit at 4 to 5 weeks after administration of the last dose of study drug, and will complete the study follow-up evaluations.

Study drug will be discontinued prematurely if any of the following protocol-specified events occur:

- The subject has a clinical AE, laboratory abnormality, intercurrent illness, or other medical condition that, in the opinion of the Investigator, makes continued administration of study drug not in the best interest of the subject. The Investigator should make a distinction between AEs that may require interruption of study drug (see Section 3.4.6) and those that require discontinuation from study drug.

- The Investigator concludes for other reasons that it is in the best interest of the subject to discontinue study drug.

- The subject requires a concomitant medication that is prohibited in the study.

- The subject wishes to withdraw consent from receiving study drug, but is willing to return for study visits.

- If pregnancy is suspected while the subject is receiving study drug, the study drug must be withheld immediately until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject will be followed for safety until outcome. In the case of pregnancy, the Investigator must immediately (within 24 hours of confirmation) notify the Sponsor of this event and record the pregnancy on the SAE report Form.

- Study drug administration will be permanently discontinued in subjects experiencing a significant safety event (See Section 3.4.3) at any time during the study.

- Study drug administration will be discontinued in subjects who experience a probably or possibly related Grade 3 toxicity (except nausea, vomiting and diarrhea that responds to treatment) that does not return to baseline or ≤ Grade 1 within two weeks of a dose adjustment or dose interruption of study drug administration.

- Significant safety event that does not resolve within 7 days of lowering the dose or a dose

interruption

• The Investigator will continue to monitor subjects who have discontinued prematurely from study drug due to an AE (serious and non serious) until resolution or stabilization of the AE.

The Investigator must complete all applicable CRF pages for subjects who discontinue study drug prematurely. Final visit procedures (i.e., AE assessment, concomitant medications review, physical exam, vital signs, weight, laboratory evaluations, ECG, and CT and PET-CT scan) should be conducted for any subject who discontinues study drug prematurely.

Subjects who prematurely discontinue study drug for any reason other than toxicity may be re-entered into the study after consultation between the Investigator and the Sponsor or the Sponsor's designee. Dosing of a subject who previously discontinued in the study is at the discretion of the Sponsor. However, subjects who drop out due to toxicity will not be replaced and will be considered a DLT, as described in Section 3.4.3.

12.0   PRODUCT SPECIFICATIONS

12.1   Description

AL3818 was designed based on computer modeling to develop a molecule that was specifically to inhibit vascular endothelial growth factor receptors (VEGFR1, VEGFR2/KDR and VEGFR3), stem cell factor receptor (C-kit), platelet derived growth factor receptor (PDGFRβ) and other kinase activity; inhibit VEGFR2-mediated downstream signal transduction, thereby inhibit tumor angiogenesis. It was later discovered to have high potency against FGFr (FGFr1, FGFr2 and FGFr3) as well as VEGFr and thus may prove to be a potent dual inhibitor.   The chemical name of AL3818 is 1-[[[4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-Yl]oxy]methyl]cyclopropanaminedihydrochloride, and the common name is anlotinib hydrochloride. The molecular formula is $C_{23}H_{22}FN_3O_3·2HCl$ and molecular weight: 480.36.

Figure 12.1-1: AL3818 (Anlotinib Hydrochloride)

AL3818 has been shown to have anti-tumor activities both in-vitro and in-vivo. The evaluation of the efficacy of AL3818 in cytotoxicity assays was conducted on 786-O, A375, A549, Caki-1,

U87MG, MDA-MB-231, HT-29, NCI-H526, HMC-1 and many other tumor cell lines in vitro. The results showed that AL3818 had an inhibitory effect on the proliferation of these cell lines in a non-cell type-specific manner. AL3818 significantly inhibited the kinase phosphorylation levels of KDR, and its activity was similar Sunitinib, but stronger than Sorafenib. AL3818 also strongly inhibited c-Kit, and PDGFRβ kinase activities at a lower IC50 than Sorafenib.

The drug product is manufactured under current Good Manufacturing Practices (cGMP) at a contract manufacturing facility that has undergone FDA inspection.

12.2 Formulation, Packaging, and Labeling

AL3818 will be supplied as 2 mg, 8 mg and 12 mg capsules packaged in PVDC heat-sealed foil-laminated blister cards of 10 tablets each and placed in boxes.

Each capsule will contain AL3818 2 mg, 8 mg and 12 mg capsules. Study drug packaging will be affixed with a single label panel containing the following information:

> AL3818 (Anlotinib hydrochloride) Capsules
> XXX mg / Capsule
> Lot Number: XXXXXX
> Manufacturing Date: MM-DD-YYYY
> Store at Controlled Room Temperature (15-25°C)
> Caution: New Drug – Limited by U.S. Federal Law to Investigational Use
> Manufactured for Advenchen Laboratories, LLC.

12.3 Receipt, Storage and Stability of AL3818

AL3818 capsules will be packaged in PVDC heat-sealed foil-laminated blister cards of 10 capsules each and placed in boxes. Excursions permitted to 0- 30 °C (32˚ to 86˚F), and after receipt should be stored at 15 - 25 °C (59˚-77˚F) [see USP Controlled Room Temperature] until use.

12.4 Preparation of Study Drug

AL3818 is supplied as a 2 mg, 8 mg or 12 mg capsule. Dosing is based on the cohort assignment. There is no manipulation or preparation of study drug other than dispensing to patients and reconciliation.

12.5 Administration of Study Drug

Study drug shall be administered in the CRU after at least 3 hours of fasting on days where subjects will be held for pharmacokinetic evaluations. On all other days, subjects may self-administer study medication at home at the same time each day, preferably in the morning prior to a light breakfast.

12.6   Ordering and Distribution of Study Drug

Please refer to your Study Procedures Manual.

12.7   Accountability of Study Drugs

All study drugs received, dispensed, and returned must be accounted for in the study drug

Dispensing Log, including:

- Subject number and initials

- Date study drug was dispensed

- Quantity dispensed

- Quantity returned

- Amount wasted (if applicable)

All study drug received and dispensed by the Investigator will be inventoried and accounted for throughout the study. The study drug must be stored in a restricted area with limited access. Contents of the study drug containers must not be combined.

The Investigator must maintain an accurate, up to date Dispensing Log for all study drugs supplied by the Sponsor. Study drug dispensed for all subjects must be recorded on the Drug Accountability Form. The study drug Dispensing Log and remaining drug inventory will be reviewed at each monitoring visit by the Sponsor-designated clinical monitor.

The study drug supplied for this study is for use only in subjects properly consented and enrolled into this protocol. Study drugs must be kept in a secure location physically separated from standard clinic or office drug supplies.

13.0   SAFETY MONITORING AND ADVERSE EVENTS

13.1   Adverse Events

Data regarding treatment-emergent AEs will be collected in this study. Treatment-emergent AEs are events that are not present at baseline, or if present at baseline, have worsened in severity.

The descriptions and grading scales found in the CTCAE v 4.03 will be used for AE reporting. A copy of the CTCAE v 4.03 is provided in Appendix B.

Definition of Adverse Events and Adverse Drug Reactions:

Adverse events in the Case Report Form (CRF) will be classified according to the most recent FDA definitions and in a manner consistent with ICH guidelines.   As such the following definitions will be used:

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product (IP) or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma). A laboratory abnormality will be reported on the "Adverse Event" case report form only if it is associated with clinical sequelae or requires therapeutic intervention. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

The reporting period for non-serious AEs starts after the first administration of study drug on Day 0 and ends 21-Days after discontinuation of study medication.

If a serious AE remains unresolved after 21-Days past study medication discontinuation, the subject will be followed, at the investigator's discretion, until resolution of the event. SAEs must be followed until resolution by the PI, even if this extends beyond the study-reporting period.

Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The investigator will assess AEs for severity, for relationship to IP, and as to whether the event meets one or more of the definitions of an SAE.

The investigator will determine the severity of each AE and will record it on the source documents and AE CRF, using the categories defined below.

The investigator will determine the relationship of an AE to the IP and will record it on the source documents and AE CRF, using the categories defined below.

A "Suspected Adverse Drug Reaction" is an event that is considered to have only possible relationship to study medication.   An "Adverse Drug Reaction" is an event that has probably or known relationship to study medication.

Category	Description
Adverse Event	Any untoward medical occurrence associated with the use of the IP, whether or not considered drug related.
Suspected Adverse Drug Reaction	Any adverse event for which there is a reasonable possibility (ie, evidence to suggest) that the IP caused the adverse event.
Adverse Drug Reaction	Any event caused by the IP (ie, there is reason to conclude that the IP caused the event).

In order to classify adverse events and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms entered on the CRF, using MedDRA.CTCAE is provided in Appendix B.

Table 13.1-1: Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 4.03)

Description of Event Intensity	Grade
Mild	1
Moderate	2
Severe	3
Life-threatening or disabling*	4
Death related to AE*	5

 *must be reported as an SAE

For those AEs that are not described on the CTCAE v 4.03, such AEs will be graded on a 3-point scale (mild, moderate, severe) and reported as indicated on the CRF. Intensity of such an AE is defined as follows:

Mild: Discomfort noticed, but no disruption to daily activity

Moderate: Discomfort sufficient to reduce or affect normal daily activity

Severe: Inability to work or perform normal daily activity

13.2   Serious Adverse Events

According to the ICH Guidelines for Good Clinical Practice (E6), an SAE is any untoward

medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death

- Is life-threatening

- Requires in-subject hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect

- Important medical events

Although not an SAE, exposure to study drug during pregnancy, even if no AE is reported in the mother, should be reported within 24 hours. For subjects who are maintained in the hospital for observation on optional in-subject study Day 2 by the investigator, but not for a significant adverse event, this additional period in the hospital for PK evaluations and observation will not be considered an SAE and is part of the normal study protocol.

13.2.1   Reporting Requirements for Serious Adverse Events

All SAEs must be reported to the Drug Safety Coordinator or the Medical Monitor, if the Drug Safety Coordinator is not available, either by telephone or facsimile, by the Investigator, study coordinator, other designated study personnel, or clinical research associate within 24 hours of notification of the SAE. Notification is requested by email with PDF of SAE reporting form and relevant information sent to dougc@advenchen.com. Follow-up information must be reported to the Drug Safety Coordinator as it becomes available. The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution.

Table 13.2-1: Contact Information for SAE Reporting

Primary Contact		Secondary Contact	
Medical Monitor		Deputy Clinical Director:	
Ethan Natelson, MD		Doug Coil	
Office:	+1-713-441-5154	Cellular:	+1 – 832-283-7705
Fax:	+1-713-793-7065		
Email:	eanatelson@att.net	Email:	dougc@advenchen.com

13.2.2   Recording of Serious Adverse Events

All SAE information must be recorded in ink on the SAE form provided by the Sponsor. Additional follow-up information (e.g., test results, autopsy, and discharge summary) must be obtained to supplement the SAE report form. A copy of all initial and follow-up reports must be filed with the subject's CRF

14.0   STATISTICAL CONSIDERATIONS

14.1   Outcome Measures

The outcome measure for Part 1 is safety of 21-day cycles of AL3818. The primary outcome measure for Part 2 is objective response rate (ORR) to determine clinical benefit and the secondary outcome measure is overall survival (OS) rate. ORR is measured by the number of partial and

complete responses (CR + PR) and clinical benefit rate is measured as CR + PR + SD (SD ≥ 16 weeks from inclusion). OS is measured from the date the study treatment was started to the date of death from any cause. OS will be estimated using the Kaplan-Meier analysis method. The study design is a Simon two-stage optimum design. Clinical benefit was defined as one of the following: confirmed PR, CR or SD by RECIST (See Appendix D) for more than 16 weeks; or non-progression for more than 16 weeks without progressive disease radiographically. If the true clinical benefit was found to be ≤ 10% in patients then AL3818 would not be considered of further interest. Patients will continue on study until cancer progression, excessive toxicities or removal from the study by either the patient or physician.

14.2   Sample Size Determination

Up to 48 subjects (up to 3 in Part 1 and 45 in Part 2) will be enrolled at up to three investigative sites. The sample size for this study is not based on statistical considerations. The initial dose of12 mg is based on nonclinical safety data and previous human experience.

14.3   Analysis Data Sets

Subjects who receive at least one dose of AL3818 will be included in the safety analyses. Subjects who complete the study visits through the final day of dosing (sixth 21-Day cycle of therapy) will be included in the primary PD and preliminary efficacy analyses.

For subjects that continue on therapy and complete additional 21-Day cycles of therapy, safety will be assessed for all subjects continuously and at time of discontinuation. Additional analyses during the compassionate use phase may be performed at the discretion of the Sponsor to assess the efficacy of the study medication.

14.4   Statistical Power Analysis

The statistical power analysis for this study was conducted using G Power software with exact Binomial Distribution. Assuming that the clinical benefit of AL3818 is 30% or more in the treated population, the power analysis is to find out the probability of rejecting the null hypothesis with our first 15 enrolled patients.   The output from the G Power shows that with 13 patients the power already reached 83.4% with actual alpha 0.0279.   Therefore, our first 15 enrolled patients will have sufficient statistical power to reject the null hypothesis.

14.5   Data Analyses

Protocol driven analyses (safety, PD, and preliminary efficacy) will be based on data through the final day of dosing in the first 21-Day continuous cycle of therapy. The primary assessment for safety of AL3818 will be conducted after the follow-up visit (7±2 days after final dose) and a study report will be prepared based on those data. Additional analyses may be conducted for subjects who have extended therapy (compassionate use) as deemed appropriate by the Sponsor, but will not be part of the formal study analyses. All subjects will be followed for safety while on medication at any time (primary study or compassionate use) and followed for 21-Days after the last dose of study medication.

For continuous variables, data distributions will be described using means, medians, and measures of dispersion such as variances and ranges. Frequencies and proportions will be tabulated for incidence and categorical variables. For parameters measured over time, data and changes from baseline will be described for each time point.

14.6   Safety

Safety data will be summarized by dose group and based on their initial dose level or treatment group (i.e. if a dose reduction occurs they will be considered in their initial group). Descriptive statistics will be provided for actual values and change from baseline values for vital signs, weight, clinical laboratory tests (serum chemistry, hematology, and urinalysis), and 12-lead ECG parameters.

The incidence and severity of AEs reported during the study and their relationship to study drug will be tabulated. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) and the CTCAE v 4.03, and will be presented by body system. The incidence of laboratory abnormalities as determined by the CTCAE v 4.03 will be summarized for each dose cohort and time point.

The World Health Organization Drug Dictionary (WHODRL) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class by dose cohort.

14.7   Pharmacokinetics

None

14.8   Pharmacodynamics

If desired, mean values of tumor marker FGFR2 will possibly be tabulated for each dose cohort at baseline and when the subject completes each three subsequent 21-Day cycles of therapy.

14.9   Preliminary Efficacy

An appropriate imaging technique for each subject at baseline and at the end of each three 21-Day cycles of therapy.   For subjects that continue on therapy after the first six 21-Day cycles, imaging studies may be repeated to assess objective response after every three additional 21-Day periods of treatment.   RECIST v 1.1 will be used to evaluate subject's progression.   All subjects with measureable disease will be followed for progressive disease (PD) according to RECIST 1.1. Subjects that have evaluable disease at baseline will be evaluated for complete response (CR), partial response (PR) or PD.

15.0   DATACOLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

15.1   Data Collection and Reporting

A CRF will be completed for each subject who receives at least one dose of study drug. All entries on the CRF must be supported by original source documentation (e.g., laboratory reports, medical records) maintained at the investigational site.

The Investigator will make all safety assessments (AEs, clinical laboratory tests, ECGs, vital signs, and results from physical examinations) on an ongoing basis. The Investigator is required to review all entries on the CRF and sign at appropriate time intervals.

15.2   Study Monitoring

All aspects of the study will be monitored carefully by the Sponsor's designees with respect to current Good Clinical Practice and Standard Operating Procedures for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including CRFs, source documents, etc., for review and inspection by the clinical monitor.

All CRFs will be 100 % source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject. Clinical monitors will evaluate periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing procedures, and the verification of the accuracy and completeness of CRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

15.3   Data Disclosure and Subject Confidentiality

Subject medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor clinical monitor (or designee), and the IRB/EC.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be identifiable only by coded numbers. Clinical information will not be released without written permission from the subject, except as necessary for monitoring by the IRB, the FDA, or the study Sponsor.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

The results of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor.

16.0   PROTECTION OF HUMAN SUBJECTS

16.1   Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the South Africa revision (1996)

16.2   Institutional Review Board/Ethics Committee

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the Informed Consent Form. The study will not be initiated until the Investigator obtains written approval of the research plan and the Informed Consent Form from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/EC complies with the requirements set forth in 21 CFR Part 56.

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Appendix A. Schedule of Study Procedures

Appendix A1: Part 1: Schedule of Study Procedures

Study Procedure	Screening/Baseline[a]	First Cycle (Days 1 to 22) - Primary Safety Evaluation				Cycle 2 Day 7	Cycle 2 Day 21	Cycle 3 Day 21	Cycle 4 Day 21	Cycle 5 Day 21	Long Term Follow-Up[b]
Study Day	-14 to -1	1	8	15	22	29	43	64	85	106	
Signed informed consent	X										
medical history	X										
complete physical exam	X				X			X			
Targeted physical exam[*]	X			X	X	X	X	X			
Vital signs	X	X[c]	X	X	X	X	X	X	X	X	
Weight	X				X		X	X			
Serum β-hCG	X										
Echocardiogram	X										
Concomitant medication assesment	X	X	X	X	X	X	X	X	X	X	
Adverse event assesment	X	X	X	X	X	X	X	X	X	X	
ECG[d]	X[d]	X[d]		X	X						
CBC, CMP, Urinalysis[e]	X[e]										
Lipid Profile, Amylase and Lipase	X				X		X	X			
Thyroid Function Test (TSH, T3 and T4)	X				X		X	X			
aPTT, INR (incl. Haptoglobin and FDPs)	X			X				X			
AL3818 Administration			X	X	X	X	X	X	X	X	
Biomarkers	X[f]			X	X			X			
ECOG Performance Assesment	X				X			X			
RECIST	X[g]										

*A targeted physical exam is defined as a limited examination for the cause and severity of a reported adverse event to assess the need for medical intervention. A general examination is not necessary.

a. Baseline evaluations must be performed within 72 hours prior to dosing on Day 8.

b. Long Term Follow-up should be performed every 30 days after calendar procedures are complete. Data should be gathered from the patient or representative as to the following – Free of Disease (FD), Living with Disease (LWD), Dead of Disease (DOD) and date, Dead of Other Causes (DOC) and date.

c. Vital signs (temperature, pulse, and blood pressure) are to be obtained just prior to dosing, and at 1, 2, 4, and 8 hours post dosing. Pulse and blood pressure will be checked prior to discharge from the CRU.

d. ECG is to be performed on Day 1, and at 60 minutes and 3-5 hours after dosing.

e. Blood samples are to be obtained within 24 hours prior to administration of the study drug. Includes RBC morphology, reticulocyte count and triglycerides (amylase and lipase).

f. Baseline values for tumor markers will be obtained within 7 days prior to initial dosing on Day 8.

g. Tumor and CNS imaging studies must be performed within 21 days prior to dosing on Day 8.

Appendix A2: Part 2: Schedule of Study Procedures

Study Procedure	Screening/ Baseline	Cycle 1 (Days 1 to 22)			Cycle 2 Day 7	Cycle 2 Day 21	Cycle 3 Day 21	Cycle 4 Day 21	Cycle 5 Day 21	Cycle 6 Day 21	Final Study Visit[a]
Study Day	-14 to -1	1	8	22	29	43	64	85	106	127	
Signed informed consent	X										
Medical history	X										
Complete physical exam	X										
Vital signs	X	X[b]	X	X		X	X				X
Weight	X	X	X	X		X	X				X
Serum β-hCG	X										
Echocardiogram	X										
Concomitant medication assesment	X						X				X
Adverse event assesment	X	X	X	X		X	X				X
ECG	X[c]						X[c]				X
CBC, CMP, Urinalysis[d]	X										
Lipid Profile, Amylase and Lipase	X			X		X	X				X
Thyroid Function Test (TSH, T3 and T4)	X			X		X	X				X
aPTT, INR (incl. Haptoglobin and FDPs)	X	X	X	X			X				X[e]
AL3818 Administration		Continuous (7 days rest/14 days dosing)									
Biomarkers	X						X				X
ECOG Performance Assesment	X						X				X
RECIST	X[f]						X[f]			X	

a. The final visit is to be scheduled at 4 to 5 weeks after the last dose of AL3818 unless the subject is being followed for a treatment-related adverse event, in which case additional monitoring may be warranted.
b. On Day 1, vital signs (temperature, pulse, and blood pressure) are to be obtained just prior to dosing, and at 1, 2 hours after dosing

c.   ECG is to be performed in triplicate. Three ECGs in triplicate will be performed on Days 1 and 64 (pre-dose, 60 minutes and 3-5 hours post-dose).

d.   Includes RBC morphology, reticulocyte count, triglycerides (amylase and lipase), urinalysis.

e.   Safety laboratory evaluations (CBC, CMP, urinalysis, coagulation profile) will be repeated at the follow-up visit only if clinically significant values were obtained at the Day 64 visit.

f.   Imaging scans (MRI or Spiral-CT) appropriate to the location of the tumor are to be performed during screening within 21 days of dosing (Day 8) on Day 64±7 days, at the end of every three 21-Day cycles of therapy.

Appendix A3: Schedule of Study Procedures: Continued Therapy Period and Final Study Visit

Study Procedure	Multiple Dosing Period (Days 1 to 22)[a]				Cycle 2 Day 7	Cycle 2 Day 21	Cycle 3 Day 21	Cycle 4 Day 21	Cycle 5 Day 21	Cycle 6 Day 21	Final Study Visit[b]	Long Term Follow-Up[c]
Week of Study	1[a]	8	15	22	29	43	64	85	106	127		
Vital signs	X		X		X	X	X				X	
Weight	X		X		X	X	X				X	
Concomitant medication assesment	X		X		X	X	X				X	
Adverse event assesment	X		X		X	X	X				X	
CBC, CMP, Urinalysis							X[d]				X[d]	
Lipid Profile, Amylase and Lipase							X				X	
Thyroid Function Test (TSH, T3 and T4)							X				X	
aPTT, INR (incl. Haptoglobin and FDPs)							X				X	
ECG[e]							X[e]					
AL3818 Administration	Dosing for 126 Days (7 days rest/14 days dosing schedule per cycle)											
Tumor Marker							X[f]				X[f]	
ECOG Performance Assesment							X				X	
RECIST[g]							X[g]					

a. For subjects who continue on therapy in Part 1 or Part 2, the Day 1 visit will be the last day of the initial 126-Day cycle of therapy.

b. The final visit is to be scheduled at 4 to 5 weeks after the last dose of AL3818 unless the subject is being followed for a treatment-related adverse event, in which case additional monitoring may be warranted.

c. Long Term Follow-up should be performed every 30 days after calendar procedures are complete. Data should be gathered from the patient or representative as to the following – Free of Disease (FD), Living with Disease (LWD), Dead of Disease (DOD) and date, Dead of Other Causes (DOC) and date.

d. Includes RBC morphology, reticulocyte count, triglycerides (amylase and lipase), and urinalysis.

e. a single ECG is to be performed. Only a single ECG is required prior to dosing on day 64.

f.   Tumor markers which are;> 2x ULN at baseline will be collected at the end of every three 21-Day cycles of therapy and at the Final Study Visit.

g.   Imaging scans (MRI or Spiral-CT) appropriate to the location of the tumor are to be performed on Day 63±7 days and at the end of each six 21-Day cycles

Appendix B. National Cancer Institute
Common Terminology Criteria for Adverse Events

Version 4.03

Publication Date: 14 June 2010

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix C. Eastern Cooperative Oncology Group Performance Scale

ECOG Performance Scale*

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50 % of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

*Oken, MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicology and response criteria of the Eastern Cooperative Oncology Group." *Am. J. Clin. Oncol.* 1982;5:649-655.

Appendix D. Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

http://ctep.cancer.gov/protocolDevelopment/docs/recistguideline.pdf

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

- Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is being evaluated.

Measurable disease - the presence of at least one measurable lesion.If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm by chest x-ray, as $\geq$ 10 mm with CT scan or MRI, or $\geq$ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable lesions - All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with $\geq$ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Methods of Measurement

- CT and PET-CT are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and PET-CT should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT or MRI should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30 % decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20 % increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition, to the relative increase of 20 %, the sum must also demonstrate an absolute increase of at least 5 mm.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)
(1) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status.	

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the subjects' files and radiological images is the best approach.

Reporting of results

- All subjects included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each subject will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

- All of the subjects who met the eligibility criteria should be included in the main analysis of the response rate. Subjects in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

- All conclusions should be based on all eligible subjects.

- Subanalyses may then be performed on the basis of a subset of subjects, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding subjects from the analysis should be clearly reported.

- The 95 % confidence intervals should be provided.

Appendix E. Strong Inhibitors and Inducers of CYP3A4, CYP2C9, and CYP2C19

CYP	Strong inhibitors (≥ 5-fold increase in AUC or > 80% decrease in CL.)	Strong Inducers (≥ 80% decrease in AUC)
3A4	Boceprevir Clarithromycin Conivaptan, Grapefruit juice[b] Indinavir Itraconazole Ketoconazole, Iopinavir/ritonavir Mibefradil[c] Nefazodone Nelfinavir Posaconazol Ritonavir Saquinavir Telaprevir Telithromycin Voriconazole	Avasimibe[g] Carbamazepine Phenytoin Rifampin St. John's wort[h]
2C9	Amiodarone Fluconazole Miconazole Oxandrolone (by definition, these 4 drugs are moderate inhibitors of CYP2C9)	Carbamazepine Rifampin
2C19	Fluconazole[d] Fluvoxamine[e] Ticlopidine[f]	Rifampin

Appendix F. New York Heart Association (NYHA) Functional Classification

The Criteria Committee of the New York Heart Association. (1994). *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.