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Clinical Trial Results

A Phase Ib Study of Lucitanib (AL3810) in a Cohort of Patients with Recurrent and Metastatic Nasopharyngeal Carcinoma

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Abstract

Background: Lucitanib is a novel multi-target inhibitor of FGFR1-3, VEGFR 1-3, and PDGFR α/β. Here, we evaluated the safety, tolerability, and preliminary efficacy of lucitanib in recurrent and metastatic nasopharyngeal carcinoma (RM-NPC).

Methods: Patients with pretreated RM-NPC were randomly divided into two treatment arms: continuous or intermittent treatment. The primary endpoint was safety and tolerability. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS).

Results: One hundred percent of patients in the continuous arm and 90% of patients in the intermittent arm had at least one treatment-related AE (TRAE). Grade ≥3 related TRAEs occurred in 5 patients in the continuous arm (5/10, 50%). No TRAEs grade >3 occurred in the intermittent arm. The ORR and DCR of the continuous arm was 20% and 90%, and the intermittent arm was 10% and 60%, respectively. All responses were observed by the first evaluation. The duration of response was more than 1 year, with two patients still on treatment with sustained response at more than 3 years.

Conclusion: Lucitanib has promising clinical activity and tolerable safety profile in heavily pretreated patients with NPC. Patients who responded to lucitanib treatment generally achieved a long DoR. Lucitanib is now being evaluated in phase II/III studies.

ClinicalTrials.gov identifier: NCT03260179

Key words: anti-angiogenic therapy; kinase inhibitor; AL3810; phase I trial; nasopharyngeal carcinoma

Lessons Learned

- Molecularly targeted therapy is a promising treatment strategy for patients with nasopharyngeal carcinoma (NPC) following tumor progression after failure of platinum-based chemotherapy.
- Preliminary data from this phase-Ib study showed that lucitanib, as a novel multi-target inhibitor of FGFR1-3, VEGFR 1-3, and PDGFR α/β, was well tolerated with favorable pharmacokinetics and showed encouraging anti-tumor activity in heavily pretreated patients with NPC.

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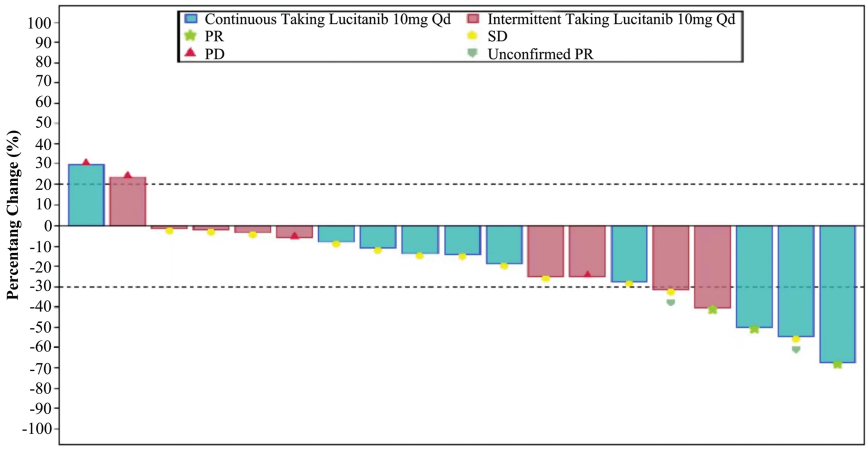

Figure 1. Waterfall plot. The percentage of tumor dimension from baseline. The response evaluation criteria was as follows: Partial response (PR) referred to at least 30% decline in tumor dimension and progressive disease >20% increase.

Discussion

Nasopharyngeal carcinoma (NPC) is prevalent in Southeast Asia, with an incidence of 20-50 cases per 100 000 people.[1] Currently, platinum-based therapy is the first-line palliative care treatment for advanced NPC patients.[2] However, there is still no standard salvageable therapeutic strategy for patients who experience failure from the original platinum-based regimen. Therefore, effective therapies for patients with advanced NPC are urgently needed. Lucitanib (AL3810), is an oral tyrosine kinase inhibitor that target fibroblast growth factor receptors 1-3 (FGFR1-3), vascular endothelial growth factor receptors 1-3 (VEGFR1-3) and the platelet-derived growth factor receptor α/β (PDGFR α/β). A phase I/IIa study has evaluated the clinical activity and adverse effects of lucitanib in patients with advanced solid tumors.[3] The results showed that, in patients with angiogenesis-sensitive disease, the ORR was 26% and the median PFS was 25 weeks, while patients with FGF-aberrant breast cancer achieved a 50% partial response with a median PFS of 40.4 weeks.[3] Other clinical trials for metastatic breast cancer and lung cancer have also demonstrated that lucitanib has promising efficacy and manageable side-effects in anti-tumor therapy.[4,5] However, there are no clinical data to evaluate the anti-tumor activity of lucitanib in advanced NPC. Here, we explore the safety profile and therapeutic efficacy of lucitanib in patients with RM-NPC.

Patients were randomly divided into two treatment groups: a continuous arm (n = 10) or intermittent arm (n = 10). All patients who received lucitanib therapy experienced at least one TEAE. Grade ≥3 related TEAEs occurred in 7 patients (7/20, 35%), including 5 patients in the continuous arm (5/10, 50%) and 2 in the intermittent arm (2/10, 20%). No patients experienced serious TRAEs. The most frequent grade ≥3 TRAEs were hypertension (30% vs 0%), proteinuria (20% vs 0%), increased AST (10% vs 0%), and decreased platelet count (10% vs 0%), in the continuous and intermittent arms, respectively—which were all on-target toxicities. With appropriate supportive treatment, dose reduction and/or temporary interruption, all TRAEs were manageable.

The therapeutic efficacy of lucitanib in patients with NPC was summarized in Figure 1. The ORR was 20% in the continuous arm and 10% in the intermittent arm. The DCR reached 90% in the continuous arm and 60% in the intermittent arm. The median PFS for patients in the continuous arm was 3.73 months (90% CI, 3.5 to NE months) and 3.68 months (90% CI, 1.74 to 7.36 months) in the intermittent arm. The PK profiles in patients with NPC were similar to a previous clinical lucitanib study.[3]

In conclusion, lucitanib once daily continuous treatment showed a manageable side-effect profile and promising efficacy in RM-NPC patients. Further safety and efficacy assessments of lucitanib are being evaluated in phase II/III studies.

Trial Information	
Disease	Nasopharyngeal carcinoma
Stage of disease/treatment	Metastatic/advanced
Prior therapy	No designated number of regimens
Type of study	Phase I, phase Ib, multi-centre, open-label
Primary endpoints	Safety, tolerability
Secondary endpoints	Objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS)
Investigator's analysis	Active and should be pursued further

Additional Details of Endpoints or Study Design

Patient Selection and Treatment

Eligible patients had histologically or cytologically confirmed NPC that had recurred at locoregional and/or distant sites that were unamenable to curative treatment. The target lesions were measured according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. All patients must have received at least one prior line of platinum-based chemotherapy for recurrent disease and had adequate organ

function. Patients underwent baseline contrast-enhanced computed tomography of the chest, abdomen, and pelvis, and magnetic resonance imaging or computed tomography scanning for locoregional disease. Radiologic assessments were performed every 8 weeks. Archived tumor samples were retrieved. Eligible patients were randomly divided into two treatment arms: continuous daily dosing on a 4-week cycle, or intermittent treatment (3 weeks on/1 week off). The treatments were terminated when patients experienced disease progression, intolerable toxicity, or death.

Assessments

Each of the two arms was evaluated separately. The primary endpoint was the safety profile. Toxicity was graded according to the Common Terminology Criteria for Adverse Event version 4.03.

The secondary endpoint was preliminary efficacy involving objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or a partial response (PR) as the best overall response, evaluated by the investigator according to the RECIST version 1.1. Other secondary endpoints included DCR and PFS. Disease control rate was defined as the proportion of patients with a confirmed CR or a confirmed PR or prolonged stable disease (SD; according to the RECIST criteria for at least 4 weeks from randomization) during treatment. Exploratory endpoints were to characterize the biological activity of lucitanib on soluble growth factors of interest, tumor cells and to explore potentially predictive responses to lucatinib in blood samples and in primary archived specimens or metastatic tumors.

This is an exploratory study. Therefore, no formal sample size calculation was carried out. This study is planned to enroll patients in five cohorts, including gastric cancer (GC), hepatocellular carcinoma (HCC), biliary tract caner (BTC), nasopharyngeal carcinoma (NPC) and thymic tumor. Each cohort is 1:1 randomized into continuous medication group or intermittent medication group. Each group of each cohort will include 10 patients, total 100 patients. The study was early terminated according to strategy adjustment. Finally, 44 patients were enrolled, including 20 NPC, 10 BTC, 6 GC, 4 HCC, and 4 thymic tumor. Here, we reported the data in a cohort of patients with recurrent and metastatic NPC.

Pharmacokinetic Analysis

In the two arms, pharmacokinetic (PK) assessment was conducted on cycle 1, day 1 (C1D1) after a single-dose administration and on cycle 1, day 15 (C1D15) after multiple-dose administrations. Blood samples were collected on day 1 and day 15 at 0 hours (predose), and then at 0.5, 1, 2, 3, 4, 8, and 12 hours post-dose, and pre-dose on C1D2, C1D16, C2D1, and C2D15. Blood samples were centrifuged and plasma frozen at a refrigeration of −80 ± 5°C until further analysis. AL3810 plasma concentrations were measured using a confirmed liquid chromatography-tandem mass spectrometry method.

Pharmacokinetic parameters after single-dose administration included: time to reach maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from 0 to 24 hours after administration ($AUC_{0\text{-}24h}$). The area under the drug concentration-time curve from 0 to the last measurable concentration ($AUC_{0\text{-}t}$), the area under the drug concentration time curve from 0 to infinity ($AUC_{0\text{-}\infty}$), terminal phase elimination rate constant (λ_z), the elimination half-life ($t_{1/2}$), apparent total clearance (CL/F), the apparent volume of distribution (V_z/F), extrapolated percentage of $AUC_{0\text{-}\infty}$ (% AUC_{ex}), and mean residence time (MRT).

Pharmacokinetic parameters after multiple-dose administrations included: steady-state peak concentration (C_{ss}, max), steady-state trough concentration (C_{ss}, min), steady-state mean plasma concentration (C_{ss}, avg), steady-state peak time (T_{ss}, max), area under the plasma concentration-time curve for steady state (AUC_{ss}), λ_z, $t_{1/2}$, steady-state apparent clearance (CL_{ss}/F), steady-state apparent volume of distribution (V_{ss}/F), fluctuation coefficient (% Fluctuation), accumulation ratio based on AUC (R_{ac}, AUC), and C_{max} (R_{ac}, C_{max}). Descriptive statistics were measured for the PK parameters using the mean with its corresponding standard deviation (SD).

Statistics and Sample Size Calculation

Patients who signed the informed consent (including failed screening and successful screening) were pooled in the inclusion set (IS). Patients in the IS who took at least one dose of lucitanib were pooled in the safety set (SS). The qualitative and quantitative results are presented as descriptive statistics. The baseline patient characteristics and safety were carried out on the SS. The efficacy was assessed in the full analysis set. The Kaplan-Meier method was used to estimate PFS. The 90% CIs were calculated for PFS to evaluate the efficacy of the two cohorts. Fisher's exact test compared the response rate in the different subgroups. Two-sided tests were applied. A P-value of $< .05$ was identified as statistically significant. All analyses were carried out using the Statistical Package for Social Science (SPSS) 23.0.

Drug Information	
Generic/working name	Lucitanib
Company name	Haihe Biopharma Co., Ltd, Shanghai, China
Drug type	Small molecule
Drug class	Angiogenesis
Dose	10 mg
Route	oral (p.o.)
Schedule of administration	Intermittent arm: 3 weeks on/1 week off Continuous arm: continuous daily dosing on a 4-week cycle

Patient Characteristics: Intermittent Arm	
Number of patients, male	8
Number of patients, female	2
Stage	i.v.(10)
Age	Median (range):43.5(20, 65)
Number of prior systemic therapies	
Performance Status: ECOG	• 0—5 • 1—5 • 2—0 • 3—0 • Unknown—0
Other	See Table 1 for detailed patient characteristics
Cancer types or histologic subtypes	Undifferentiated NPC 10

Patient Characteristics: Continuous Arm	
Number of patients, male	7
Number of patients, female	3
Stage	IV(9); unknown(1)
Age	Median (range):45.5(25, 52)
Number of prior systemic therapies	
Performance status: ECOG	• 0—7 • 1—3 • 2—0 • 3—0 • Unknown—0
Other	See Table 1 for detailed patient characteristics
Cancer types or histologic subtypes	Undifferentiated NPC 10

Primary Assessment Method: Intermittent Arm	
Title	**Efficacy**
Number of patients screened	10
Number of patients enrolled	10
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10
Evaluation method	RECIST 1.1
Response assessment CR	*n* = 0 (0%)
Response assessment PR	*n* = 1 (10%)
Response assessment SD	*n* = 5 (50%)
Response assessment PD	*n* = 3 (30%)
Response assessment OTHER	*n* = 1 (10%)
(Median) duration assessments PFS	3.68 months

Outcome Notes

See Figure 1, Figure 2, and Table 4 for detailed response data.

Tables 2 and 3 summarize adverse events. Figs. 1 and 2, and Table 4 report detailed response data.

Primary Assessment Method: Continuous Arm	
Title	**efficacy**
Number of patients screened	10
Number of patients enrolled	10
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	10

Title	efficacy
Evaluation method	RECIST 1.1
Response assessment CR	*n* = 0 (0%)
Response assessment PR	*n* = 2 (20%)
Response assessment SD	*n* = 7 (70%)
Response assessment PD	*n* = 1 (10%)
Response assessment OTHER	*n* = 0 (0%)
(Median) duration assessments PFS	3.73 months

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

For patients with advanced NPC, combination therapy with cisplatin and 5-fluorouracil is the most frequently used first-line regimen, with a high response rate of 66-78% and a median PFS of 11-14 months. Recently, the first phase III trial for RM-NPC, the landmark GEM20110714 study, established gemcitabine plus cisplatin (GP) as the standard first-line treatment.[6] However, for patients with RM-NPC, there is no suitable second-line treatment regimen to choose from after failure of the platinum-based first-line treatment. Therefore, an effective second-line therapy is urgently needed for this group of patients.

Molecularly targeted therapy mainly involves drugs that bind to oncogenes to inhibit tumor progression and angiopoiesis. They have been widely explored in RM-NPC. One of them is axitinib. Axitinib is a potent VEGFR inhibitor reported to achieve a 19% ORR and 78.4 DCR in 37 recruited patients with RM-NPC, with a median PFS and an overall survival (OS) of 5 and 10 months, respectively.[7] Another is apatinib, which was evaluated in 51 relapsed and refractory patients with NPC who had no response to first- or second-line chemotherapy. The results demonstrated an ORR of 31.4% (16/51), with a median PFS of 9 months and OS of 16 months.[8] A phase II study also investigated the treatment efficacy of pazopanib in 33 patients with NPC. The ORR was 6.1% and the DCR was 54.5% at 3 months.[9] Famitinib was also reported in a phase II trial to achieve an ORR of 6.9%, a DCR of 32.8% at 3 months and a median PFS of 3.2 months in 58 NPC patients as reported in an abstract.[10] Although these therapeutic agents showed a modest response rate in NPC patients, all these reports were single arm, had a small sample size, were exploratory trials, and most of them were investigator initiated. In a systematic review, aggregating estimates of OS and PFS for RM-NPC in first- and second-line or higher treatment settings, for patients in the second-line and beyond, current therapies only had moderate antitumor activity with ORRs ranging from 0% to 48% with a median PFS of 5.2-5.4 months and a median OS of 11.5-12.5 months.[11]

Our study is the first to investigate the safety and therapeutic efficacy of lucitanib in patients with RM-NPC. Our results show that lucitanib has potential efficacy in NPC. In patients receiving continuous lucitanib treatment, we observed an objective response in 20% of patients and disease control in 90% of patients, and the median PFS was 3.73 months (90% CI, 3.5 to NE months). In all three of the responders, a PR was obtained at the first evaluation and lasted more than 1 year. Two of them were still on treatment (as of the cutoff date of the last follow-up), with a sustained response of more than 3 years. Overall, lucitanib demonstrated potently promising therapeutic activity and high disease control. Thus, lucatinib might be a potential treatment option for NPCs.

Identifying effective tumor response biomarkers helps doctors to screen patients for potential clinical benefits, which aligns with the personalized tumor treatment paradigm. Previous studies have shown that FGFR1 or FGF amplification may be a biomarker for lucitanib therapy in advanced cancers. A phase I/IIa study reported that the ORR in patients with FGF-aberrant (FGFR1- or FGF3/4/19-amplified) breast cancer reached 50% and the median PFS was 40.4 weeks, which was superior to those with angiogenesis-sensitive solid tumors (ORR of 26% and PFS of 25 weeks). Angiogenesis-sensitive refers to a histological tumor type that responds to antiangiogen-based therapy or develops new progression after at least 6 months of stability.[3] AL3810 is a multi-angiogenic tyrosine kinases inhibitor that significantly targets VEGFR, FGFR, and PDGFR kinases. Its targets are similar to erdafitinib (FGFR-1 to FGFR-4, VEGFR-2, and PDGFR-α/β).[12] A study of molecular assays has shown that AL3810 and sorafenib showed similar potency against VEGFR2 and PDGFR, but AL3810 was more potent against FGFR than sorafenib.[13] Another clinical trial in HR+/HER2-metastatic breast cancer demonstrated that lucitanib achieved a higher ORR in patients with high FGFR1 amplification than those without high amplification (22% vs. 9%). Given that VEGFR was overexpressed in 60% of clinical NPC samples and associated with a poor prognosis,[14] further explorations of the biomarker are warranted to identify patients who may benefit from lucitanib treatment.

A recent study found that an early decrease in plasma EBV DNA copy number correlated with a favorable response of RM-NPC patients treated with immunotherapy,[15] which is consistent with previous reports showing that the dynamic changes in EBV titer are closely related to chemotherapy and radiotherapy response.[16,17] Although we collected baseline plasma EBV-DNA information when patients enrolled in our study, unfortunately we did not monitor this change, especially when patients responded or progression occurred. Dynamic EBV-DNA changes need further exploration as a predictor of lucitanib treatment efficacy in RM-NPC patients.

According to previous studies, a continuous 15 mg daily dose was unsustainable beyond three cycles due to arterial hypertension related to the antiangiogenic effect of lucitanib,

as such the dose was reduced to 10 mg.[3,4] Following these results, we selected 10 mg as the treatment dose in this study and randomly divided the patients into two cohorts: continuous daily treatment or intermittent treatment (3 weeks on/1 week off). The most frequent treatment-related AE (TRAEs) grade ≥3 were hypertension (30% vs 0%), proteinuria (20% vs 0%), increased AST (10% vs 0%), and decreased platelet count (10% vs 0%), which is similar to other clinical lucitanib studies.[3,4,18-20] This suggests that intermittent treatment could significantly improve the safety profile of lucitanib in patients with NPC. With suitable supportive treatment, dose reduction and/or temporary discontinuation, all TRAEs grade ≥3 can be effectively managed. Hypothyroidism was also one of the most common TRAEs in NPC patients (60% vs 50%), which is consistent with the toxicity profile of other multitarget tyrosine kinase inhibitors such as sunitinib,[21] but it can be easily managed with thyroid hormone supplementation.

Lucitanib was rapidly absorbed with a median Tmax of 1.00 and 2.02 hours in the continuous and intermittent arms, respectively. The observed trough levels suggest that the steady state is reached by day 15. At the steady state, lucitanib exposure (C_{max}, AUC0-24h) was approximately two to three times of that on day 1. Detailed pharmacokinetic parameters are listed in Tables 5 and 6. The PK parameters of lucitanib in NPC patients were consistent with those in a previous clinical lucitanib study,[3] which supports lucitanib once daily administration.

In conclusion, continuous once daily lucatinib treatment showed promising clinical activity in RM-NPC patients. Patients who responded lucitanib generally achieved a long duration of response. Although the TRAE grade ≥3 for continuous treatment was numerically higher than intermittent treatment, all the AEs were on target side effects, which were predictable and manageable. While our sample size was comparatively small and the overall survival data was immature for analysis our results merit further evaluation in follow-up studies.

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Conflict of Interest

The authors indicated no financial relationships.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures and Tables

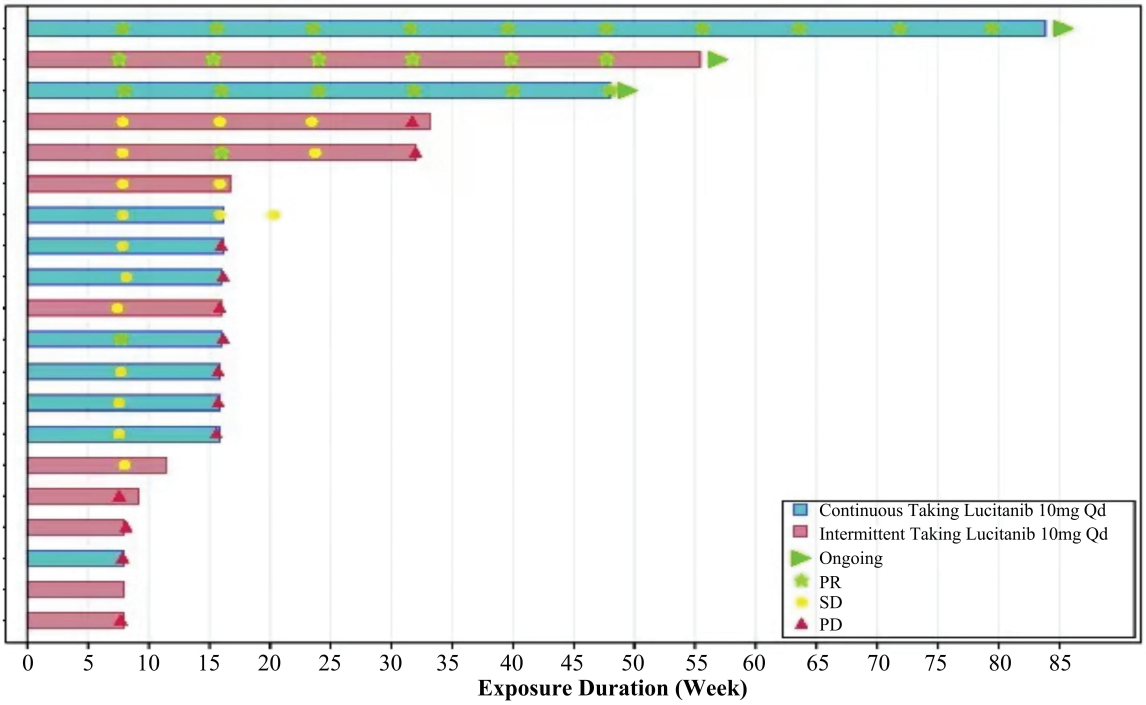

Figure 2. Swimmer plot. Duration of response and time to response in patients receiving Lucitanib. CR, complete response; PD, progressive disease; PR, partial response.

Table 1. Baseline characteristics of enrolled NPC patients.

Characteristics	Continuous arm (*n* = 10)	Intermittent arm (*n* = 10)
Age, years, median, (max, min)	45.5 (25, 52)	43.5 (20, 65)
Sex (male/female)	7/3	8/2
ECOG status (0/1)	7/3	5/5
Histology (WHO)	Undifferentiated NPC	Undifferentiated NPC
Distant metastasis (no/yes)	1/9	0/10
Time since diagnosis, years, median	4.0 (1.0, 9.0)	3.0 (2.0, 9.0)
TNM stage at primary diagnosis		
IIIA	1 (10%)	1 (10%)
IIIB	0	0
IV	4 (40%)	6 (60%)
Unknown	3 (30%)	3 (30%)
TNM stage when study started		
IIA	0	0
IV	9 (90%)	10 (100%)
Unknown	1 (10%)	0
Previous lines of therapy		
1	4 (20%)	4 (20%)
2	3 (30%)	2 (20%)
≥3	3 (30%)	4 (40%)
EBV-DNA status		
Positive	7	5
Negative	1	3
Missing	2	2

NPC, nasopharyngeal carcinoma; TNM, tumor node metastasis classification; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

Table 2. Drug-related adverse events with an incidence >10% in all patients.

Preferred term	Continuous arm (*n* = 10) *n* (%)	Intermittent arm (*n* = 10) *n* (%)
All	10 (100.0)	9 (90.0)
Hypertension	10 (100.0)	4 (40.0)
Proteinuria	10 (100.0)	5 (50.0)
Hypothyroidism	6 (60.0)	5 (50.0)
AST increased	4 (40.0)	0
TSH increased	3 (30.0)	1 (10.0)
Backache	4 (40.0)	0
Diarrhea	3 (30.0)	0
Skin rash	3 (30.0)	0
Epistaxis	5 (50.0)	4 (40.0)
Hypochloremia	3 (30.0)	1 (10.0)
Weight loss	4 (40.0)	0
Serum creatinine (Scr) increased	4 (40.0)	1 (10.0)
Platelet count decreased	3 (30.0)	1 (10.0)
Free thyroxine decreased	3 (30.0)	1 (10.0)
Cough	2 (20.0)	3 (30.0)

Table 3. The summary of TEAEs and TRAEs in continuous arm and intermittent arm.

Adverse events *n* (%)	Continuous arm (*n* = 10) *n* (%)	Intermittent arm (*n* = 10) *n* (%)
Any grade TEAE	10 (100)	10 (100)
Grade ≥3 TEAE	5 (50)	2 (20)
Grade ≥3 TRAE	5 (50)	0
Serious TRAE	0	0
TRAE lead to dose reduction	4 (40)	0
TRAE lead to dose interruption	5 (50)	2 (20)
TRAE lead to dose discontinuation	0	1 (10)

TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events.

Table 4. Summary of antitumor activities of lucitanib.

Best response *n*(%)	Continuous arm (*n* = 10) *n* (%)	Intermittent arm (*n* = 10) *n* (%)
PR	2 (20)	1 (10)
SD	7 (70)	5 (50)
PD	1 (10)	3 (30)
ORR	20%	10%
DCR	90%	60%

Table 5. The PK parameters of AL3810 from single-dose administration.

PK parameters	Statistics	Continuous arm (n = 5)	Intermittent arm (n = 4)
C_{max} (ng/mL)	Mean ± SD	293.20 ± 139.58	254.00 ± 147.86
	GeoMean(%CVb)	260.62(64.42)	227.86(55.29)
T_{max} (hour)	Median	1.00	2.02
	Min, max	0.50, 2.00	0.50, 2.95
$AUC_{0\text{-}24h}$ (ng*hour/mL)	Mean ± SD	2558.30 ± 857.95	3109.42 ± 1887.72
	GeoMean(%CVb)	2405.22(44.55)	2772.60(56.26)
$AUC_{0\text{-}t}$ (ng*hour/mL)	Mean ± SD	2513.64 ± 833.77	3026.47 ± 1754.46
	GeoMean(%CVb)	2366.10(44.09)	2723.82(53.79)
CL/F (L/hour)	Mean ± SD	2.44 ± 1.5048	2.24 ± 1.21
	GeoMean(%CVb)	2.15(57.72)	1.83(105.30)
V_z/F (L)	Mean ± SD	75.22 ± 40.20	60.82 ± 19.84
	GeoMean(%CVb)	68.00(51.77)	58.08(37.66)
λ_z (1/hour)	Mean ± SD	0.03 ± 0.01	0.03 ± 0.01
	GeoMean(%CVb)	0.03(45.08)	0.03(55.97)
$t_{1/2}$ (hour)	Mean ± SD	23.79 ± 11.81	24.78 ± 15.46
	GeoMean(%CVb)	21.93(45.08)	22.05(55.97)
$\%AUC_{ex}$ (%)	Mean ± SD	48.16 ± 10.87	47.96 ± 15.75
	GeoMean(%CVb)	47.22(22.24)	46.33(29.69)
MRT (hour)	Mean ± SD	34.20 ± 14.29	36.28 ± 21.57
	GeoMean(%CVb)	32.21(38.53)	32.65(52.83)

Table 6. The PK parameters of AL3810 from multiple-dose administration.

PK parameters	Statistics	Continuous Arm (n=5)	Intermittent Arm (n=4)
$C_{ss,max}$ (ng/mL)	Mean ± SD	482.80 ± 271.81	608.50 ± 169.48
	GeoMean(%CV_b)	435.78(50.87)	590.42(29.26)
$C_{ss,min}$ (ng/mL)	Mean ± SD	203.46 ± 93.47	303.00 ± 117.86
	GeoMean(%CV_b)	176.24(77.90)	284.37(44.50)
$C_{ss,avg}$ (ng/mL)	Mean ± SD	277.72 ± 109.76	403.39 ± 154.68
	GeoMean(%CV_b)	257.16(49.01)	381.64(40.16)
$T_{ss,max}$ (hour)	Median	2.97	1.98
	Min, Max	0.95, 4.00	0.93, 4.00
AUC_{ss} (ng*hour/mL)	Mean ± SD	6665.30 ± 2634.20	9681.40 ± 3712.42
	GeoMean(%CV_b)	6171.82(49.01)	9159.28(40.16)
λ_z (1/hour)	Mean ± SD	0.02 ± 0.01	0.02 ± 0.01
	GeoMean(%CV_b)	0.01(99.37)	0.02(55.07)
CL_{ss}/F (L/hour)	Mean ± SD	1.78 ± 0.93	1.15 ± 0.45
	GeoMean(%CV_b)	1.62(49.01)	1.09(40.16)
V_{ss}/F (L)	Mean ± SD	163.32 ± 140.17	55.84 ± 17.90
	GeoMean(%CV_b)	125.47(94.88)	53.61(34.32)
%Fluctuation (%)	Mean ± SD	104.26 ± 61.47	81.15 ± 21.54
	GeoMean(%CV_b)	90.75(63.71)	79.03(27.10)
$R_{ac,AUC}$	Mean ± SD	2.62 ± 0.55	3.38 ± 0.84
	GeoMean(%CV_b)	2.57(22.45)	3.30(25.14)
$R_{ac,Cmax}$	Mean ± SD	1.98 ± 1.20	2.67 ± 0.69
	GeoMean(%CV_b)	1.67(77.55)	2.59(29.36)
$R_{Cmin,D15}$	Mean ± SD	0.99 ± 0.3410	1.00 ± 0.28
	GeoMean(%CV_b)	0.94(34.42)	0.97(27.66)