Thyroid

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Anlotinib for the Treatment of Patients With Locally Advanced or Metastatic Medullary Thyroid Cancer

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Abstract

Background: The prognosis of advanced or metastatic medullary thyroid carcinoma (MTC) is poor and there are few therapeutic options. Anlotinib has previously shown promising antitumor activity on MTC in preclinical models and a phase I study. This phase II clinical trial was devised to confirm the anti-tumor activity of anlotinib in patients with advanced or metastatic MTC.

Methods: Patients with unresectable locally advanced or metastatic MTC received once daily oral anlotinib 12 mg, 2 weeks on/ 1 week off, until disease progression, death, unacceptable toxicity or withdrawal of consent for any reason. The dose was adjusted on the basis of observed toxicity. The primary endpoint was progression free survival (PFS).

Results: Fifty-eight patients received anlotinib treatment. The primary endpoint PFS has not yet been reached by the time of analysis. On the basis of investigator assessments, 56.90% of patients experienced a partial response. Progression free survival rate at 48 weeks was 85.5%. 45 patients had a 50% or greater decrease in serum calcitonin concentration from baseline. The most common adverse events were hand-foot syndrome, hypertriglyceridemia, cholesterol elevation, fatigue and proteinuria.

Conclusions: Anlotinib demonstrated a durable antitumor activity with a manageable adverse event profile in locally advanced or metastatic MTC.

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Introduction

Medullary thyroid carcinoma (MTC), originating from the thyroid C cells producing calcitonin, is a rare neuroendocrine tumor accounting for 0.6%-2% of all thyroid cancers (1, 2). In unselected patients with MTC, the 10-year overall survival rate is approximately 75%, however, it decreases to 40% or less in patients with locally advanced or metastatic disease (3). MTC presents as sporadic (4) or hereditary tumor in the context of multiple endocrine neoplasia type 2 (5, 6), and the latter is frequently accompanied by pheochromocytoma and hyperparathyroidism (7).

The only way to cure MTC is the complete resection of thyroid tumor and any loco-regional metastases (2, 8). For progressive or symptomatic metastatic MTC that cannot be treated with local management, systemic therapy should be considered. However, traditional cytotoxic agents, such as 5-fluorouracil, doxorubicin, dacarbazine and cyclophosphamide, showed limited efficacy but significant toxicity (2, 9, 10).

One of the validated therapeutic targets for MTC is the RET oncogene (11, 12), which is mutated in the germline in almost all of the patients with hereditary MTC (6, 13), and 50% to 60% of the patients with sporadic MTC harbor somatic *RET* gene mutations (14, 15). Besides, angiogenesis plays a crucial role in the growth and dissemination of thyroid cancer cells. Vascular endothelial growth factor receptors (VEGFR-1 and VEGFR-2) (16, 17), as well as fibroblast growth factor (FGF)/fibroblast growth factor receptor (FGFR), are frequently over-expressed in MTC tumor cells and vascular endothelium (18-20).

Vandetanib and cabozantinib, small molecular inhibitors that target RET and VEGFR-2, provide therapeutic efficacy in MTC by blocking both angiogenic and proliferative pathways (3, 21-23). Both vandetanib and cabozantinib have been approved by the Food and Drug Administration (FDA) for treating MTC. Unfortunately, neither has been approved for MTC treatment in China. Many other tyrosine kinase inhibitors such as lenvatinib, motesanib and axitinib (among others) have shown various degrees of activity in phase II clinical trials (24-26).

Anlotinib is a novel tyrosine kinase inhibitor targeting multiple receptor kinases involved in tumor proliferation, vasculature, and tumor microenvironment (27). Anlotinib

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inhibits VEGF/VEGFR signaling by selectively targeting VEGFR2/3 and FGFR1-4 with high affinity. Anlotinib also suppresses the activity of platelet-derived growth factor receptor (PDGFR) α/β, c-Kit and RET, showing significant inhibition of tumor proliferation (27). In preclinical experiments, anlotinib showed broad antitumor activity against a variety of xenograft models (27, 28).

In a phase I study, anlotinib showed manageable toxicity and broad-spectrum antitumor potential. Anlotinib at doses from 5 mg to 16 mg was administered to patients with solid tumors once a day in two schedules: four consecutive weeks (4/0) or 2-week on/1-week off (2/1) (27). Dose-limiting toxicity (DLT) was grade 3 hypertension at 10 mg in the 4/0 schedule, and grade 3 hypertension and grade 3 fatigue at 16 mg in the 2/1 schedule. Pharmacokinetic assessment indicated that the half-life of anlotinib at 12 mg in the 2/1 schedule was 116 hours. The maximum tolerated dose, 12 mg once daily in the 2/1 schedule, was chosen for the expanding the study. The main serious adverse effects were hypertension, hypertriglyceridemia, hand-foot syndrome and increased lipase levels (27).

Based on these promising results, we performed this phase II study to assess the antitumor effect of anlotinib in patients with locally advanced or metastatic MTC. Moreover, the tolerability of anlotinib in MTC was also evaluated.

Materials and methods

Study design and participants

In this single-arm phase 2 study, we enrolled patients at eight institutions across China. This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. All patients provided written informed consent to participate in the study. Pathology materials (tumor blocks or representative slides) were centrally evaluated.

Key eligibility criteria included age between 18 to 70 years, histologically confirmed unresectable or metastatic MTC, at least one measurable lesion by CT scan according to RECIST v1.1, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, life expectancy of at least 3 months, calcitonin serum levels ≥ 500 pg/ml; adequate bone

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marrow, renal, hepatic and cardiac function checked within 7 days before start of study drug, as evidenced by the following: **a.** Absolute neutrophil count (ANC) ≥ 1500/mm^3, **b.** Platelets ≥ 80,000/mm^3, **c.** Hemoglobin ≥ 10.0 g/dL (without blood transfusion within 14 days), **d.** Serum creatinine ≤ 1.0×upper limit of normal (ULN), **e.** Bilirubin ≤ 1.25×ULN, **f.** AST and ALT ≤ 1.5×ULN (≤ 5.0×ULN for patients with liver involvement), **g.** Fasting triglycerides ≤ 3.0 mmol/L, **h.** Fasting cholesterol ≤ 7.75 mmol/L, **i.** Doppler ultrasound confirmed left ventricular ejection fraction ≥ 50%. Women of childbearing potential and male patients must agree to use adequate contraception during the study participation and up to 6 months following completion of therapy.

Patients were excluded if they met any of the following criteria at the time of screening: had received a prior treatment of anti-angiogenic agents including sunitinib, sorafenib, bevacizumab, imatinib and apatinib; reported a previous or concomitant malignancy, which probably affects life expectancy, except curative skin basal cell carcinoma and cervical carcinoma *in situ*; received chemotherapy or radiotherapy within 28 days before start of initiation of the study therapy; participated in other clinical trial within 28 days before start of initiation of the study therapy; had an ongoing toxicity > Grade 1 according to NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v. 4.0); unable to swallow oral medications, any malabsorption condition; had a known history of brain or meningeal metastasis and spinal compression; was diagnosed with severe or uncontrolled disease including any of the following: symptomatic congestive heart failure, unstable angina (angina symptoms at rest) and myocardial infarction within 6 months before start of Day 1 of treatment ; severe or uncontrolled cardiac arrhythmias; uncontrolled hypertension (systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg); active or uncontrolled infection; known history of liver cirrhosis, decompensated liver diseases and chronic active hepatitis; poorly controlled diabetes (fasting blood-glucose > 10 mmol/L); spot urine with 2+ or more protein and a 24-hour urine collection with a total protein excretion > 1000 mg/24 hours; a non-healing wound, ulcer, or bone fracture; evidence or history of disease with bleeding potential or therapeutically treated with an anticoagulant agent such as warfarin, heparin or analogue; arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein

thrombosis, or pulmonary embolism; known history of human immunodeficiency or organ allograft; lactation or women with a positive pregnancy test in blood or urine within 7 days before initiation of the study therapy.

The trial was approved by the institutional review board of each participating institution and conducted in accordance with guidelines for good clinical practice and the Declaration of Helsinki. All patients provided written informed consent. The trial was registered at clinical.gov (registration number: NCT01874873).

Procedures

Eligible patients received oral anlotinib 12 mg, once daily, 2 weeks on/ 1 week off, until disease progression (RECIST 1.1 guidelines), death, unacceptable toxicity or withdrawal of consent for any reasons. During the treatment period, assessments of the tumor status were performed every six weeks.

Dose modifications for adverse events were done according to the protocol. Clinical assessments of safety, including medical history, physical examination and laboratory tests, were done every 3 weeks during the first 24 weeks and then at 6-week intervals thereafter. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria for adverse events (version 4.0). All patients were followed until death from any cause or withdrawal of consent. The primary endpoint was progression-free survival (PFS) according to RECIST 1.1. Secondary endpoints were objective response rate (ORR), disease control rate (DCR) at 24 weeks, overall survival (OS), biochemical response (change of serum calcitonin levels from baseline) and safety.

Statistical analysis

Disease control rate at 24 weeks associated with best supportive therapy and anlotinib in patients with locally advanced or metastatic MTC was determined as 50% and 70%, respectively. A Simon two-stage testing procedure was applied with type I error of 5% and type II error of 20% each (α=0.05, β=0.2). On the basis of optimal design principle, 15 patients were enrolled in the first stage. If 8 of the 15 patients did not have disease progression at 24 weeks, 28 patients were further enrolled in the second stage. If 26 of 43

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patients did not show disease progression at 24 weeks, the result would be positive. A surplus recruitment of five patients was allowed to correct for ineligible or untreated patients. In this study, another ten eligible patients were enrolled after getting approval from the institutional review board.

Progression-free survival was defined as the time from treatment initiation to the date of disease progression or death from any cause, whichever came first. Patients alive at the time of analysis were censored at the date of last disease assessment. Overall survival was measured from the date of treatment initiation to the date of death (from any cause). PFS and OS were estimated using the Kaplan-Meier survival curves. ORR was defined as the proportion of patients who had a partial or complete response. DCR was defined as the proportion of patients who had achieved complete response, partial response or stable disease at 24 weeks.

The following patient populations were considered in the final analyses. Full analysis set (FAS): All patients who were eligible and had started their allocated treatment (at least one dose of the study drug); Per protocol set (PPS): All patients who were eligible and received their allocated treatment at least 6 weeks; Safety set (SS): All patients who had started treatment (at least one dose of the study drug).

Role of the funding source

This clinical trial was funded by the Jiangsu Chia-tai Tianqing Pharmaceutical Co., Ltd. The funders had no role in the design, data collection and analysis. The corresponding author had full access to the data and took final responsibility for the decision to submit for publication.

Results

Between July 2013 and July 2014, fifty-eight eligible patients were accrued to this study. The final data analysis was carried out in July 2016. Table 1 contains baseline characteristics of patients. The median age was 46.9 years old (range 22–71). 93.1% of the patients underwent surgery, 25.9% received radiotherapy and 12.1% received chemotherapy before study entry. 89.7% of the patients were diagnosed with metastatic

medullary thyroid carcinoma. The most common metastatic sites were lymph nodes, lung and liver.

All patients started treatment according to protocol. Three patients were excluded from the PPS because lack of target lesions (n=2), or retreat from study within one week (n=1). Therefore, 58 patients were included in FAS and SS, and 55 patients were included in PPS. All 58 patients were treated, receiving a total of 908 cycles (median: 16, range 1–30).

Efficacy

The median follow-up time was 9.8 months. In the FAS, the objective response rate was 56.90% (33/58; 95% CI: 44.15-69.64; Figure 1). The disease control rate was 93.1% (54/58; 95% CI: 88.09-99.58). Durable stable disease was observed in most patients, and the PFS rate at 24 weeks, 36 weeks and 48 weeks were 92.2%, 87.8% and 84.5%, respectively. The median PFS has not yet been reached by the time of analysis (Figure 2A). The survival rate at 12 months, 24 months and 36 months were 89.7%, 78.6% and 76.4%, respectively. The median OS has not yet been reached by the time of analysis (Figure 2B).

Calcitonin response

Calcitonin response at week 12 was evaluable in 51 patients (87.9%). The most common reason that patients were not evaluable was the lack of a week-12 assessment. Significant decreases from baseline in serum calcitonin (≥50%) occurred in 45 patients (57.5%). In the 33 patients who achieved PR, 22 had significant calcitonin decreases ranging from 96.9% to 50.7%.

Toxicity

The median duration of anlotinib therapy was 12 months (range 0.75-22.5 months). All patients were evaluable for toxicity. Six patients (10%) discontinued treatment because of an adverse event. Table 2 summarizes adverse events that occurred in anlotinib-treated patients (>15%). The most common adverse events (all grades, ≥30%) included hand-foot syndrome (79.31%), hypertriglyceridemia (46.55%), elevated cholesterol levels (43.1%),

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fatigue (41.38%), proteinuria (39.66%), hypertension (39.66%), sore throat (37.93%), diarrhea (34.48%), and anorexia (34.48%). The most common Grade 3 adverse events (≥3%) included: hand-foot syndrome (8.62%), hypertension(5.17%), hypertriglyceridemia (3.45%), elevated cholesterol levels (3.45%), and an increased direct bilirubin (DBIL) (3.45%). No grade 4 or 5 adverse event was recorded. Asymptomatic Grade 1 or 2 QTc prolongation was observed in two patients, which subsequently normalized without further treatment.

AEs were generally managed with dose interruptions and dose reductions. 20.7% (12/58) of anlotinib-treated patients had dose reductions. Seven serious adverse events were reported but only one lacunar infarction was considered by the investigator to be probably related to anlotinib.

Discussion

Given its rarity, it is challenging to enroll MTC patients in clinical trials. Currently, only vandetanib and cabozantinib have been approved for MTC treatment by the FDA. However, due to lack of clinical evidence to support their use in Chinese patients, both vandetanib and cabozantinib have not been approved in China. Anlotinib has demonstrated promising antitumor effects in patients with MTC in a phase I study (27). The phase 2 study presented here further confirms the antitumor activity of anlotinib in patients with locally advanced or metastatic MTC. Partial remissions were observed in 56.90% of the patients, and the disease progression free rate at 48 weeks was 85.5%. Besides, the biochemical response rate for calcitonin was 57.7%. All these data suggested clinically meaningful tumor control. The overall survival data cannot be determined as of yet, and the final assessment will be done when 50% of patients have died.

It is notable that approximately 80% of the patients included in this anlotinib study were naïve to any systemic treatment, and they reflect a patient population with relatively indolent disease compared to those with progressive disease after one or more systematic treatment(s). This may partly explain the similar antitumor effect of anlotinib in this study with vandetanib in a phase III study, which included a comparable patient population (3). In contrast, the phase III study of cabozantinib enrolled patients with pretreated and

progressive MTC and showed a lower ORR of 28% and a shorter median PFS of 11.2 months (21).

Treatment with anlotinib was generally well tolerated. The majority of adverse events were manageable according to standard clinical practice alone or in combination with anlotinib dose interruptions or dose reductions. The high frequency of lipid metabolism dysfunction including hypertriglyceridemia and cholesterol elevations was consistent with safety data in the phase I study of anlotinib, most of which were asymptomatic and reversible. However, careful monitoring of lipids is required.

The toxicity profile of anlotinib was different compared to that of cabozantinib and vandetanib. Diarrhea was the most common adverse event with these drugs and occurred in over 50% of the patients treated with the two agents (3, 21, 23). In contrast, only 22.4% of the patients receiving anlotinib experienced diarrhea, typically of grade 1 or 2 severity. QTc prolongation was one of the most common grade 3 or 4 adverse events for vandetanib, which was observed in 8% of patients in the experimental arm (3), whereas only two patients receiving anlotinib were found to have asymptomatic grade 1 or 2 QTc prolongations, and both subsequently normalized without further treatment.

In conclusion, anlotinib demonstrated promising efficacy, as well as a manageable adverse event profile in this study, which suggests that anlotinib might provide a novel effective therapeutic option for patients with advanced or metastatic MTC.

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Disclosure Statement

The authors declare that they have no competing interests.

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Table 1. Demographic and Baseline Clinical Characteristics of Patients

Characteristics	Patients	
	No.	%
Age		
Median (years)	46.9	
Range (years)	22-71	
Sex		
Male	34	58.6
Female	24	41.4
ECOG PS		
0	26	44.8
1	30	51.7
2	2	3.5
Radiation history		
Yes	15	25.9
No	43	74.1
Chemotherapy history		
Yes	7	12.1
No	51	87.9

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Other antitumor therapy		
Yes	9	15.5
No	49	84.5
Surgery history		
Yes	54	93.1
No	4	6.9
Disease stage		
Locally advanced	6	10.3
Metastatic disease	52	89.7
Metastatic site		
Lymph nodes	44	75.9
Lung	26	44.8
Liver	16	27.6
Bone	5	8.6

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status

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Table 2. AEs observed in anlotinib-treated patients (> 15%)

Events	Total		Grade 1/2		Grade 3	
	N	%	N	%	N	%
Hand-foot syndrome	46	79.31	41	70.69	5	8.62
Hypertriglyceridemia	27	46.55	25	43.10	2	3.45
Cholesterol elevation	25	43.10	23	39.66	2	3.45
Fatigue	24	41.38	23	39.66	1	1.72
Proteinuria	23	39.66	22	37.93	1	1.72
Hypertension	23	39.66	20	34.48	3	5.17
Sore Throat	22	37.93	22	37.93	0	0.00
Diarrhea	20	34.48	19	32.76	1	1.72
Anorexia	20	34.48	20	34.48	0	0.00
DBIL increased	15	25.86	13	22.41	2	3.45
ALT increased	14	24.14	13	22.41	1	1.72
TSH increased	14	24.14	14	24.14	0	0.00
TBIL increased	14	24.14	14	24.14	0	0.00
Abdominal pain	12	20.69	12	20.69	0	0.00
Cough	12	20.69	12	20.69	0	0.00
Voice alteration	12	20.69	12	20.69	0	0.00
AST increased	12	20.69	12	20.69	0	0.00
LDL increased	11	18.97	11	18.97	0	0.00

Hyperglycemia	11	18.97	11	18.97	0	0.00
Hypothyroidism	10	17.24	10	17.24	0	0.00
Stomach pain	10	17.24	9	15.52	1	1.72
Hematuria	10	17.24	10	17.24	0	0.00
Toothache	10	17.24	10	17.24	0	0.00
Colitis	9	15.52	9	15.52	0	0.00
Arthralgia	9	15.52	9	15.52	0	0.00
Leukopenia	9	15.52	9	15.52	0	0.00

Abbreviation: TSH, thyroid stimulating hormone; DBIL, Direct Bilirubin; ALT, alanine aminotransferase; TBIL, total bilirubin; LDL, low density lipoprotein

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Figure legends

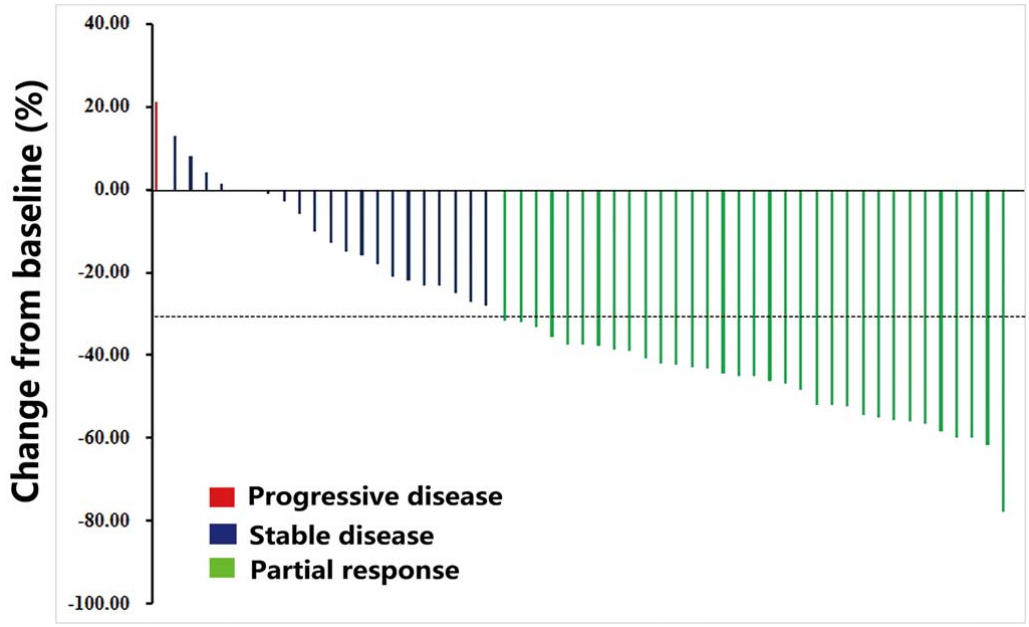

Figure 1. Tumor shrinkage per investigator review

Maximum reduction from baseline (or smallest increase from baseline for patients with no reductions) in the sum of the longest diameters of target lesions. The change from baseline in tumor measurement as assessed by investigator review is shown for 55 patients (PPS). The gray line represents the threshold for partial response (>30% reduction from baseline sum of longest diameters). Target lesions were defined according to RECIST 1.1.

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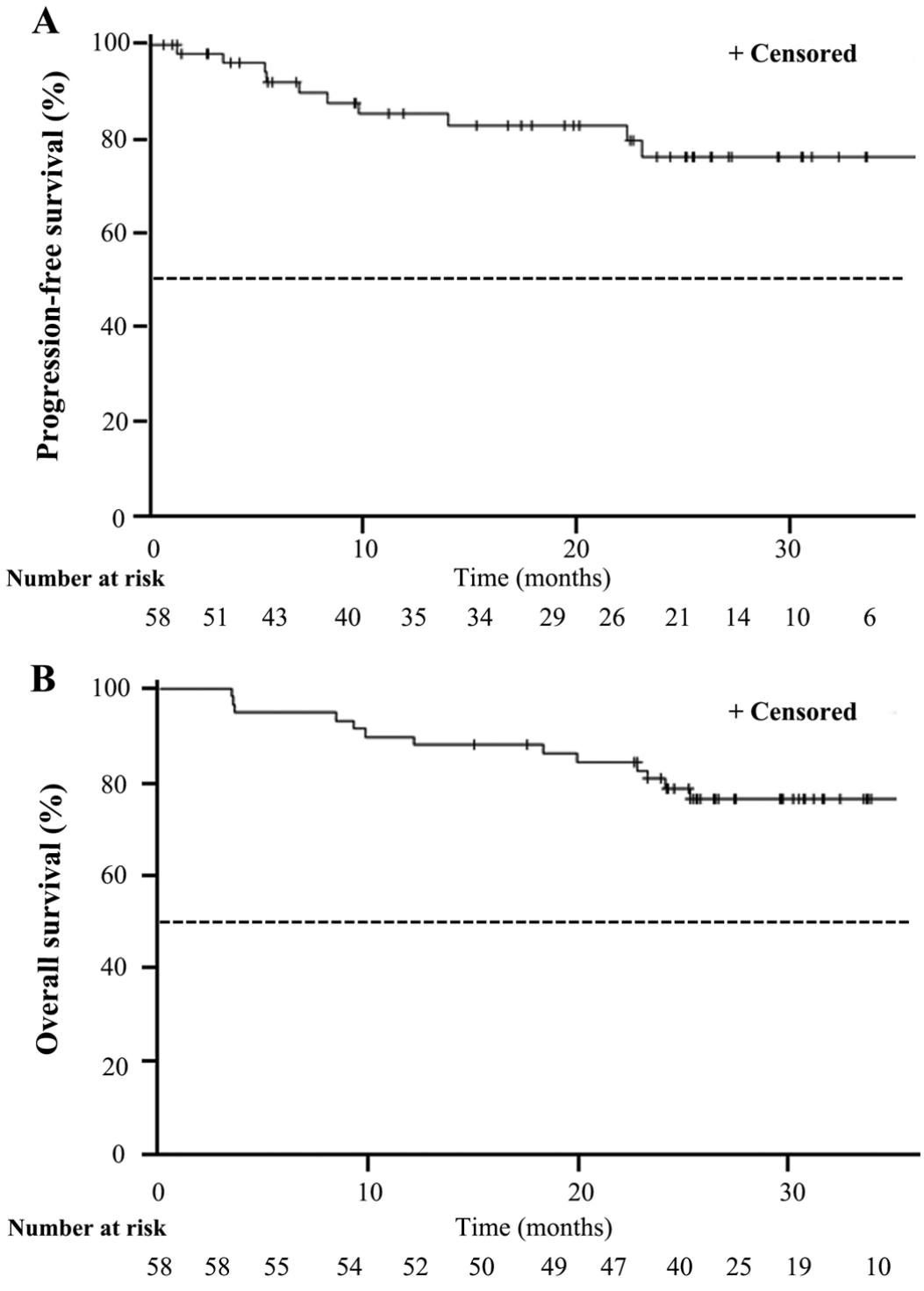

Figure 2. Kaplan-Meier curve of progression-free survival and overall survival

The dotted lines represent the threshold of 50% for PFS rate or OS rate.