Anlotinib in Locally Advanced or Metastatic Radioiodine-Refractory Differentiated Thyroid Carcinoma: A Randomized, Double-Blind, Multicenter Phase II Trial

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ABSTRACT

Purpose: Alhough antiangiogenic agents are the bedrock of treatment for radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC), novel antiangiogenic agents with optimized features like greater target-binding affinities and more favorable pharmacokinetics profile are needed. This phase II randomized, double-blind, placebo-controlled trial investigated the efficacy and safety of anlotinib, a multikinase inhibitor, for RAIR-DTC.

Patients and Methods: Patients (ages between 18 and 70 years) with pathologically confirmed locally advanced or metastatic RAIR-DTC were enrolled and randomly received 12 mg anlotinib once daily or placebo on day 1 to 14 every 3 weeks. Patients on placebo were allowed to receive open-label anlotinib after disease progression. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS) and safety.

Results: Between September 2015 and August 2018, 76 and 37 patients randomly received anlotinib and placebo, respectively. Patients receiving anlotinib had a significantly longer median PFS [40.5 months, 95% confidence interval (CI), 28.3–not estimable (NE) versus placebo 8.4 months, 95% CI, 5.6–13.8; HR = 0.21, 95% CI, 0.12–0.37, $P < 0.001$], meeting the primary endpoint. OS was still immature, with a trend of benefit with anlotinib (HR = 0.57, 95% CI, 0.29–1.12). All patients in the anlotinib group experienced adverse events (AE); 8 (10.5%) discontinued treatment due to AEs.

Conclusions: Anlotinib demonstrated promising efficacy and favorable tolerance in the treatment of locally advanced or metastatic RAIR-DTC, supporting further research to establish its role in the treatment of this serious disease.

Introduction

Radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC) is the most common cause for disease–specific mortality of thyroid cancer, with a 3-year overall survival (OS) rate less than 50% (1, 2). Currently, targeting angiogenesis is the principal treatment for RAIR-DTC and available multitarget anti-angiogenic agents include sorafenib, lenvatinib, cabozantinib (3–8). Although neurotrophic-tropomyosin receptor kinase (NTRK) inhibitors, larotrectinib

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Translational Relevance

In this randomized, double-blind, placebo-controlled trial, we investigated the efficacy and safety of anlotinib, an antiangiogenic multikinase inhibitor, in adults with locally advanced or metastatic radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC). The study met its primary endpoint, with an approximately 80% reduction in the risk of progression in patients receiving anlotinib 12 mg once daily with a two-week on, one-week off regimen versus those on placebo. In addition, 10.5% patients discontinued anlotinib treatment due to AEs. Although antiangiogenic agents are the bedrock of treatment for RAIR-DTC, novel antiangiogenic agents with optimized features like greater survival benefits and better safety profile are needed. Anlotinib as a novel antiangiogenic agent has demonstrated promising antitumor activities and an acceptable safety profile in this trial, leading to its approval for treatment of this serious disease in China. It has the potential to be a valuable addition to the armamentarium against locally advanced or metastatic RAIR-DTC.

and entrectinib and RET inhibitors, including selpercatinib and pralsetinib, have been approved for *TRK*-positive and *RET* fusion–positive DTC, respectively, *NTRK* fusions are reported in 2.3%–3.4% of adult patients and *RET* fusion occurs in only approximately 7% patients with DTC (7–13). Overall, antiangiogenic agents are still the bedrock of RAIR-DTC treatment and novel antiangiogenic agents with optimized features such as greater target-binding affinities and more favorable pharmacokinetics profile are still needed.

Anlotinib, a novel multikinase inhibitor, suppresses angiogenesis and tumor cell proliferation simultaneously by blocking VEGFR, FGFR, PDGFR and c-Kit. Despite having a similar spectrum of targets to lenvatinib, anlotinib has stronger antiangiogenic activities than lenvatinib, with an extremely low half-maximal inhibitory concentration (IC_{50}): 0.2 nmol/L for VEGFR-2 (lenvatinib 4 nmol/L) and 0.7 nmol/L for VEGFR-3 (lenvatinib 5.2 nmol/L; ref. 14). Anlotinib also has a long elimination half-life of 96 hours and is given on a two-week on, one-week off regimen, thus offering a more convenient dosing schedule than lenvatinib that is given once daily (15, 16). In a previous randomized trial, anlotinib led to a significant extension of progress-free survival (PFS) from 11.1 months to 20.7 months in patients with advanced medullary thyroid carcinoma (17). This trial was performed to investigate the efficacy and safety of anlotinib for locally advanced or metastatic RAIR-DTC.

Patients and Methods

Patients

Eligible patients were ages between 18 and 70 years and had pathologically confirmed locally advanced or metastatic RAIR-DTC. Key inclusion criteria included an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 or 1, at least one measurable lesion per RECIST v1.1 and adequate organ function. Tumor progression prior to enrollment was evaluated by the investigators and radiological evidence of progressive disease was not mandatory. Radioiodine-refractory disease was established if at least one of the following criteria was met: at least one measurable lesion without iodine uptake on any iodine-131 (^{131}I) scan, at least one measurable lesion that had progressed per RECIST v1.1 within 18 months after ^{131}I therapy, and cumulative activity of ^{131}I that was ≥600 mCi (22 GBq). Patients who had received prior anlotinib or VEGFR-targeted agents were excluded. The full trial protocol is available in Supplement 1.

Study design and treatment administration

This was a multicenter, double-blind, placebo-controlled phase II trial. Participants were randomized in a 2:1 ratio to receive 12 mg anlotinib (Chia-tai Tianqing Pharmaceutical Co., Ltd.) orally once daily or placebo on day 1 to 14 every 3 weeks. Treatment was continued until disease progression, death, or unacceptable toxicities occurred. The dose was reduced to 10 or 8 mg at the discretion of the investigator per the study protocol on dose modifications. Generally, dose reduction was recommended if grade 3 or 4 AEs occurred. No dose increase was allowed after reduction. Patients whose disease progressed per RECIST v1.1 were unblinded and patients in the placebo group were allowed to receive open-label anlotinib. Emergency unblinding was done for patients with toxicities or complications that required unblinding for management. All remaining patients were unblinded on July 3, 2020. Best supportive care was provided.

This study used a center-based randomization method, with all centers having access to the randomization system to receive participant number and drug distribution. The investigator, sponsor, and patients were blinded to treatment allocation throughout the trial.

Outcomes

Tumor response was evaluated by the Independent Radiological Review Committee (IRRC) per RECIST v1.1 every 6 weeks. Complete (CR) and partial response (PR) must be confirmed at least 4 weeks later. The primary endpoint was PFS, calculated from the date of randomization to the date of IRRC-confirmed disease progression or death, whichever occurred first. The secondary endpoints included objective response rate (ORR), OS and quality of life (QoL). ORR was defined as the proportion of patients who achieved CR or PR. DCR (disease control rate) was the percentage of patients who achieved CR, PR, or stable disease (SD) lasting for at least 4 weeks. OS was calculated from date of randomization to the date of death for any reason. QoL was assessed only in patients who were still receiving blinded treatment using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; ref. 18).

Safety data were collected over the course of treatment and until one month after the final dose. Adverse events (AE) were assessed per NCI CTC AE version 4.0 (CTCAE 4.0).

Statistical analysis

On the basis of the DECISION study of sorafenib, we assumed that anlotinib treatment would lead to a 46% decrease in HR for disease progression, corresponding to a 5-month improvement in median PFS from 5.8 months to 10.8 months (3). Hence, a sample size of 81 patients (54 in the anlotinib group and 27 in the placebo group) was required to provide an 80% power to demonstrate efficacy with a one-tailed test at a significance level of 0.05. The maximum estimated target sample size was 108 based on a dropout rate of 25%. Statistical analysis was undertaken using SAS version 9.42.

In the protocol, the plan was to assess efficacy based both on the modified intention-to-treat (mITT) set and the Per-protocol Set (PPS). However, for presenting the results of this trial, the primary analysis of efficacy would be PFS based on the mITT set. The results of the PPS analysis were provided briefly to show consistency. The mITT population included all eligible patients who had received at least one dose of anlotinib or placebo, and the PPS included eligible patients

who did not have major violation of the study protocol, completed at least 6 weeks of treatment, underwent efficacy evaluation, and showed good compliance. PFS and OS were estimated using the Kaplan–Meier method and compared by the log-rank test. HR was assessed by the Cox proportional hazards model. PFS events were censored at the date of randomization for patients with no baseline radiological evaluation, or who had no postbaseline radiological evaluation and were alive before the first scheduled radiological evaluation. PFS events were censored at the date of the final radiological evaluation for patients who did not develop progressive disease (PD) or who were alive at the end of the study. Furthermore, PFS events were censored at the date of the most recent radiological assessment for patients who had received new antitumor therapy before progression. In addition, PFS events were censored at the last radiological evaluation for patients who discontinued treatment due to nondocumented PD, toxicities, or other causes. Finally, PFS events were censored at the most recent radiological assessment for patients who had PD or died after missing two or more consecutive radiological evaluations. OS events were censored at the date of death, the final follow-up, or at the time of withdrawal. To adjust the potential bias from crossover, adjusted OS of the placebo group was also calculated based on a two-stage method derived from the rank preserving structural failure time (RPSFT) model per preplanned analysis (19). ORR and DCR were compared between groups using the χ^2 test.

The safety set included all patients who received at least one dose of the study drug and had one safety assessment. The incidence of AEs was compared between groups by the Fisher exact test. EORTC QLQ-C30 scores were repeated measurements and after the raw data were standardized, a model was established using the Generalized Estimating Equation (GEE). Exchangeable correlation structures were selected using a working correlation matrix and were used for intergroup comparison, comparison of data at different timepoints, and trends of change between groups.

For simplicity and clarity, all reported *P* values and 95% confidence intervals (CI) were two-sided and comparisons that were associated with a (two-sided) *P* value of 0.05 or less were called significant, as opposed to "statistically significant at the 0.05 level."

Study approval

The study protocol was approved by the ethics committee of each center. The trial was conducted in accordance with the Declaration of Helsinki. Participants or their legal guardians provided written informed consent. This study is registered with Clinicaltrial.gov, NCT02586337. The study was sponsored by Chia-tai Tianqing Pharmaceutical Co., Ltd. The sponsor played no role in the study design, data collection, and analysis.

Data availability

The data generated in this study are available upon request from the corresponding authors

Results

Patients

Between September 2015 and August 2018, 146 patients were screened and 113 were enrolled. Seventy-six patients who received anlotinib and 37 who received placebo were included in the mITT population and safety set. The placebo group had a significantly higher percentage of females (78% vs. 57%; $P = 0.040$). In addition, the placebo group had a significantly higher sum of the longest diameter of all target lesions (medians: 65.2 mm vs. 37.9 mm; $P = 0.040$) and a greater proportion of patients whose sum of target lesion sizes at baseline was ≥60 mm than the anlotinib group (58% vs. 36%; $P = 0.026$). The two groups were comparable in other baseline characteristics (**Table 1**; Supplementary Table S1).

Unblinding was done on July 3, 2020. At the data cutoff (January 1, 2020), 28 patients (37%) in the anlotinib group and 5 patients (14%) in the placebo group were still under treatment. The

Table 1. Patient demographic and baseline characteristics.

Characteristics	Anlotinib (*N* = 76)	Placebo (*N* = 37)
Median (IQR) age, years	56.0 (50.5–63.0)	57.0 (51.0–64.0)
Female sex[a]	43 (57)	29 (78)
ECOG-PS score		
0	34 (45)	14 (38)
1	42 (55)	23 (62)
History of surgery		
Yes	76 (100)	37 (100)
No	0	0
History of chemotherapy		
Yes	3 (4)	4 (11)
No	73 (96)	33 (89)
History of radiotherapy		
Yes	14 (18)	5 (14)
No	62 (82)	32 (86)
History of radioiodine therapy		
Yes	74 (97)	37 (100)
No	2 (3)	0
Histologic subtypes		
Papillary	69 (91)	32 (86)
Follicular	7 (9)	5 (14)
Median (IQR) sum of the longest diameter of all target lesions, mm[b]	37.9 (26.5–74.3)	65.2 (36.5 to ∼87.0)
Sum of target lesion sizes at baseline, mm[c]		
≥60	27 (36)	21 (58)
<60	49 (65)	15 (42)
Missing	0	1
Nontarget lesions		
Yes	75 (99)	37 (100)
No	1 (1)	0
Locoregional disease	8 (11)	4 (11)
Metastatic lesions		
Pulmonary metastases	72 (95)	36 (97)
Bone metastases	20 (26)	11 (30)
Liver metastases	2 (2.6)	1 (2.7)
Brain metastases	0 (0)	1 (2.7)
Radioiodine uptake before enrollment		
Yes	44 (58)	23 (62)
No	32 (42)	14 (38)
Prior cumulative RAI dose ≥ 600 mCi or 22GBq		
Yes	29 (38)	10 (27)
No	47 (62)	27 (73)
Disease progression within 3 months before randomization		
Yes	52 (71)	25 (69)
No	21 (29)	11 (31)
Missing	3	1
Disease progression within 12 months before randomization		
Yes	62 (85)	29 (81)
No	11 (15)	7 (19)
Missing	3	1

Note: Data are expressed as *N* (%) unless otherwise specified.
Abbreviation: RAI, radioactive iodine.
[a]$P = 0.040$.
[b]$Z = 2.05$, $P = 0.040$.
[c]Exact test, $P = 0.026$.

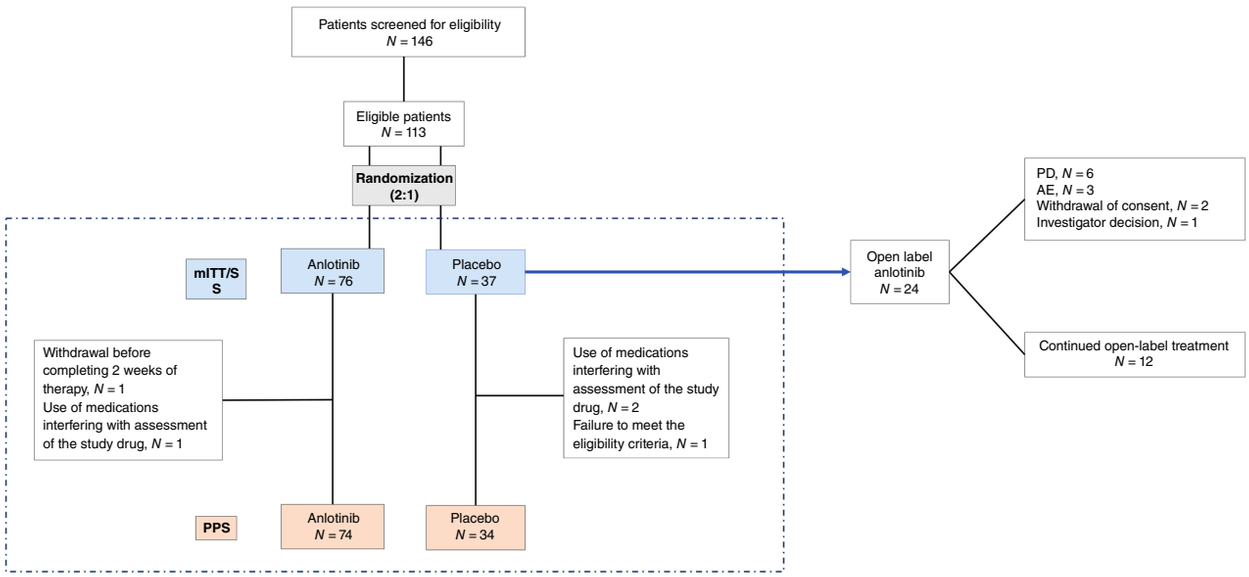

Figure 1.

CONSORT diagram of patients randomized to receive treatments of anlotinib or placebo. SS indicates safety set. Note: Three subjects in the placebo group were excluded from the PPS, including 1 who was found to have no target lesion after a subsequent review of radiological records prior to enrollment by the Independent Radiological Review Committee (IRRC), 1 who had received Kanglaite injection (a Chinese medicinal herb) for 10 days and thalidomide for 35 days, and another who had received thymopentin for 23 days, compound oxymatrine injection for 13 days and recombinant IL2 for 416 days. One subject in the anlotinib group who had received *Brucea javanica* oil emulsion for 27 days and lentinan injection for 27 days was excluded from the PPS.

median duration of treatment for patients in the two groups was 24.4 months (IQR 13.3, 37.3) and 8.1 months (IQR 5.3, 14.0), respectively ($P < 0.001$). Forty-eight patients in the anlotinib group discontinued treatment, and the causes were disease progression (24/48, 50%), death (2/48, 4%), AEs (8/48, 17%), withdrawing consent (10/48, 21%) and others (4/48, 8%). By contrast, 32 (87%) patients in the placebo group discontinued their study treatment, mostly (28/32, 88%) for disease progression. Other reasons for treatment termination were death (2/32, 6%) and AEs (2/32, 6%; **Fig. 1**).

Efficacy

In the mITT, the median duration of follow-up for PFS by the reverse Kaplan–Meier estimator was 35.9 months (95% CI, 30.3–41.5). The study successfully met its primary endpoint that the median PFS was 40.5 months [95% CI, 28.3–not estimable (NE)] in the anlotinib group, which was significantly longer than that in the placebo group (8.4 months; 95% CI, 5.6–13.8, $P < 0.001$). The HR was 0.21 (95% CI, 0.12–0.37; **Fig. 2A**). PFS benefit with anlotinib was largely consistent across different subgroups stratified by demographic and clinical characteristics, and the observed HR was less than 0.55 in all the subgroups (**Fig. 2B**). Notably, 52 patients (71%) in the anlotinib group and 25 patients (69%) in the placebo group had radiographic progressive disease within 3 months before randomization. The median PFS was not reached (95% CI, 31.0–NE) in patients receiving anlotinib versus 6.9 months (95% CI, 4.1–11.3) in patients on placebo (Supplementary Fig. S1A). Anlotinib led to a longer PFS than placebo among patients who had no evidence of radiographic progressive disease within 3 months before randomization (26.9 months, 95% CI 22.7–NE vs. 14.2 months, 95% CI 5.6–NE) though the increase was statistically not significant (Supplementary Fig. S1B). In addition, 91 patients had radiographic progressive disease within 12 months before randomization [62 (85%) in the anlotinib group and 29 (81%) in the placebo group]. Anlotinib significantly improved the PFS of these patients versus placebo (not reached, 95% CI, 31.0–NE vs. 8.4 months, 95% CI, 4.1–14.0; Supplementary Fig. S1C). Although anlotinib was associated with a numerically longer PFS versus placebo, the trend was not significant between the two groups of patients who had no radiographic progressive disease within 12 months before randomization (anlotinib 26.9 months, 95% CI, 16.8–29.5 vs. placebo 6.9 months, 95% CI, 1.3–NE; Supplementary Fig. S1D). In our trial, multivariable analysis showed that anlotinib improved the PFS of patients after adjustment for sex (female vs. male), age (≥55 vs. <55 years), ECOG-PS score (0 vs. 1), and histologic subtypes (papillary vs. follicular; HR = 0.16, 95% CI 0.09–0.31, $P < 0.001$; Supplementary Table S2).

The PPS included 74 patients in the anlotinib group and 34 patients in the placebo group. The median PFS was 36.5 months (75% CI, 28.3-NE) in the anlotinib group *versus* 7.6 months (95% CI, 5.6–14.0) in the placebo group (HR 0.22, 95% CI, 0.13–0.39, $P < 0.001$; Supplementary Fig. S2).

At the data cutoff, OS data were still immature. In the mITT, 26% of patients in the anlotinib group and 38% of patients in the placebo group died. The median OS was not reached in the anlotinib group (95% CI, 50.7–NE) *versus* 52.8 months (95% CI, 24.8–NE) in the placebo group ($P = 0.098$; **Fig. 3A**). Multivariable Cox regression analysis showed that ECOG-PS was the only independent prognostic factor of OS in both the mITT (HR = 2.42; 95% CI, 1.06–5.54; $P = 0.036$) and the PPS (HR = 2.64; 95% CI, 1.11–6.30), $P = 0.029$; Supplementary Table S3). Subgroup analysis showed that anlotinib conferred significant OS benefit on patients who were female sex, had an ECOG-PS score of 1, received prior radiotherapy, had baseline serum TSH ≤ 0.5 mU/L, or had bone metastasis (**Fig. 3B**). Meanwhile, patients with or without radiographically confirmed disease progression within 3 or 12 months before randomization derived no

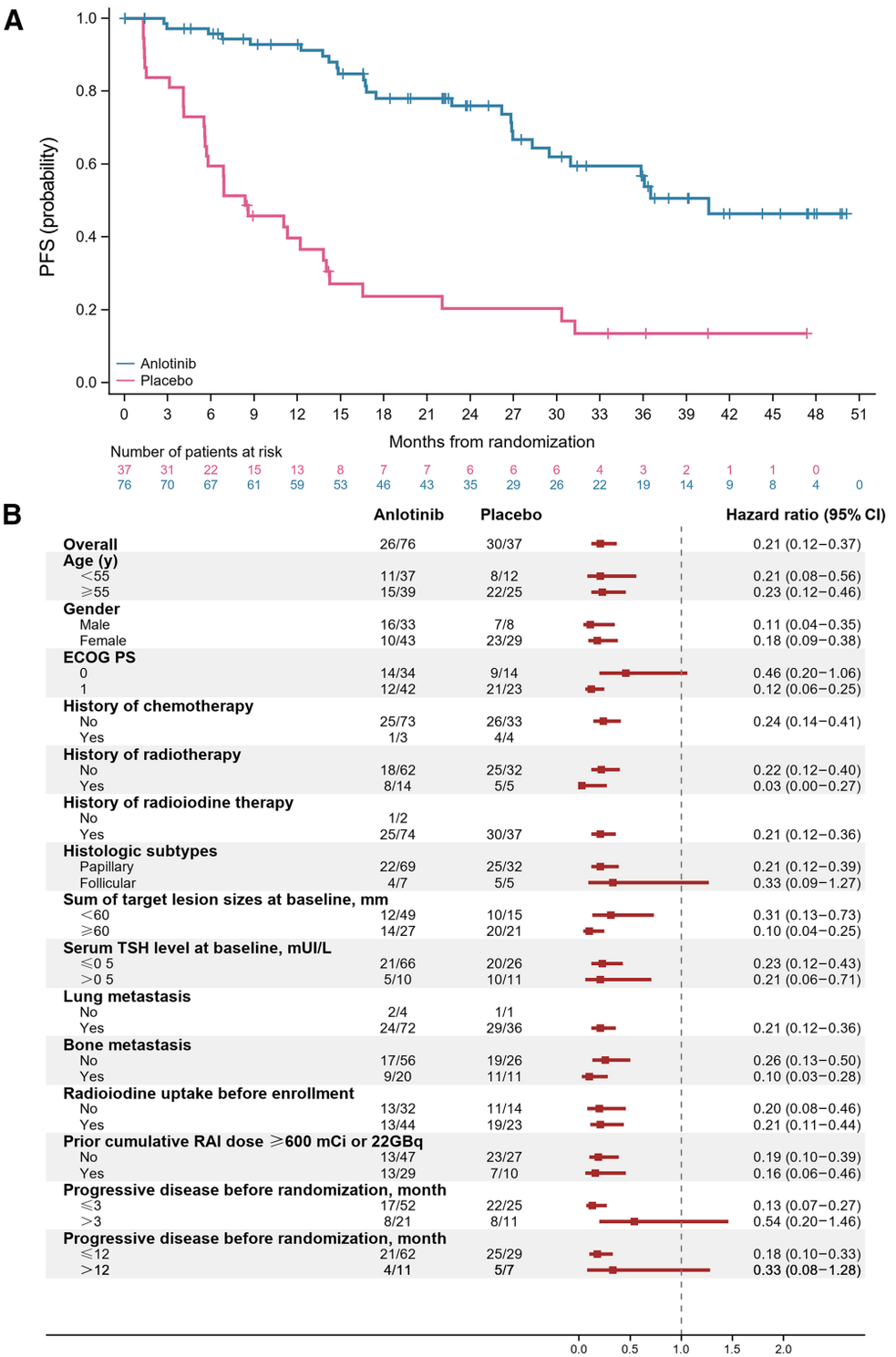

Figure 2.

A, Kaplan–Meier estimate of PFS in the intention-to-treat population. The tick marks indicate censored data. **B,** Forest plots for PFS.

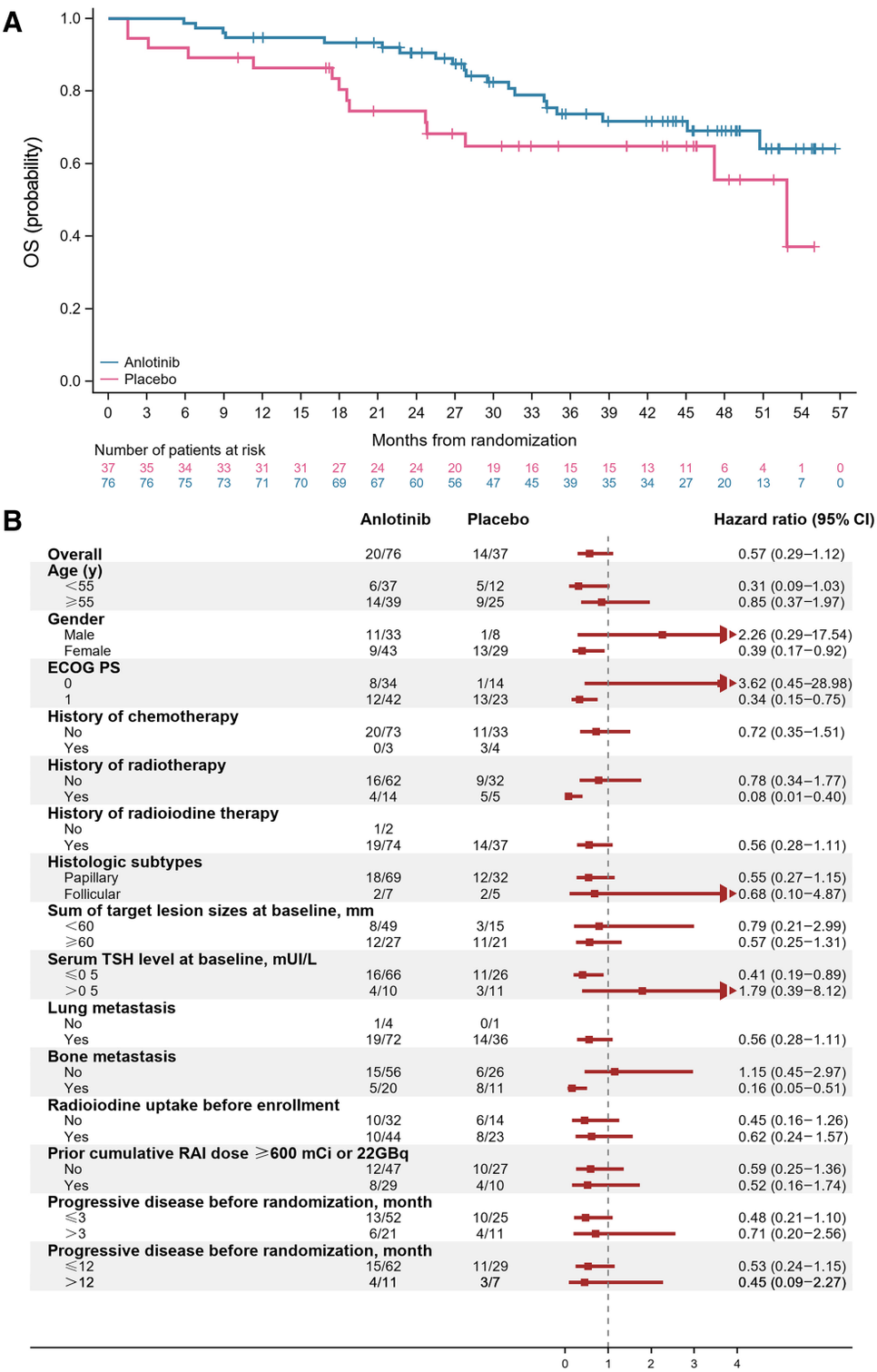

Figure 3.
A, Kaplan–Meier estimate of OS in the modified intention-to-treat population. The tick marks indicate censored data. **B,** Forest plots for OS.

significant OS benefit from anlotinib therapy versus placebo (Supplementary Fig. S3A–3D).

In the PPS, the median OS was not reached in the anlotinib group (95% CI, 50.7–NE) versus 52.8 months (95% CI, 24.8–NE) in the placebo group [HR = 0.59 (0.29–1.22), $P = 0.148$; Supplementary Fig. S4A]. Anlotinib reduced the risk of death by 43%, suggesting an unequivocal trend of OS benefit (HR, 0.57; 95% CI, 0.29–1.12) although statistical difference was not achieved. In addition, 86% (24/28) of patients in the placebo group received open-label anlotinib after disease progression, which may result in a bias favorable to the placebo group. The *post hoc* adjustment by a two-stage estimation method analysis using the RPSFT model suggested an improvement in OS for anlotinib treatment, with a HR of 0.36 (95% CI, 0.18–0.73; Supplementary Fig. S4B).

In the anlotinib group, tumor shrinkage was observed in nearly all (72/76, 95%) patients (Supplementary Fig. S5). In the mITT, 45 patients (59%) achieved confirmed PR and no patients achieved CR in the anlotinib group; the ORR was 59.2%. No tumor response was observed in the placebo group. Twenty-nine patients in each group had SD lasting for at least 4 weeks. In the mITT, the DCR was significantly higher in the anlotinib group than that in the placebo group (97.4% vs.78.4%, $P = 0.002$). The tumor response to anlotinib was durable; the median duration of response was not reached (95% CI, NE–NE) and 57% of the patients still maintained response at 36 months.

Twenty-four (86%) patients in the placebo group received open-label anlotinib. At the data cutoff date, 6 patients developed progressive disease. The median duration of follow up was 22.0 months (95% CI, 5.6–38.5) and the median PFS was not reached (95% CI, 15.9–NE). Although the patients received open-label anlotinib after radiographic progressive disease, they still had poorer survival outcomes as 10 of them (42%) died before the data cut-off date. We further compared the OS of patients who received open-label anlotinib after disease progression in the placebo group (delayed intervention) and patients in the anlotinib group who had radiographic disease progression within 12 months before randomization. Patients who had received early intervention tended to have more OS benefits; the HR was 0.53 (95% CI, 0.24–1.15, $P = 0.101$).

Safety

All patients received safety assessment. In the anlotinib group, 8 patients (11%) permanently terminated treatment due to AEs and 26 patients (34%) experienced dose reduction, compared with 9 patients (24%) and 1 patient (3%) in the placebo group, respectively. The main reasons for dose reduction included palmar-plantar erythrodysesthesia syndrome ($N = 7$, 9%), hypertension ($N = 6$, 8%), and proteinuria ($N = 4$, 5%).

The incidence of treatment related adverse events (TRAE) of all grades in the double-blind stage was 100% in the anlotinib group and 87% in the placebo group ($P = 0.003$; **Table 2**). The most common TRAEs in the two groups included hypertension (84% vs. 46%), palmar-plantar erythrodysesthesia syndrome (74% vs. 3%) and proteinuria (65% vs. 16%). Grade 3 or higher TRAEs occurred in 58 and 7 patients in two groups, respectively ($P < 0.001$). In the anlotinib group, the most common grade 3 or above TRAEs were hypertension (43%) and palmar-plantar erythrodysesthesia syndrome (20%). Grade 3 or above TRAEs are listed in Supplementary Table S4. The incidence of treatment-related serious adverse events

Table 2. TRAEs with an incidence ≥15%.

	Anlotinib ($N = 76$)		Placebo ($N = 37$)	
TRAEs	**Any grades**	**Grade ≥3**	**Any grades**	**Grade ≥3**
Hypertension	64 (84)	33 (43)	17 (46)	1 (3)
Palmar–plantar erythrodysesthesia syndrome	56 (74)	15 (20)	1 (3)	0
Proteinuria	49 (65)	3 (4)	6 (16)	1 (3)
Hypertriglyceridemia	48 (63)	7 (9)	15 (41)	0
Fatigue	34 (45)	4 (5)	4 (11)	0
Diarrhea	34 (45)	0	4 (11)	0
Hypercholesterolemia	33 (43)	0	7 (19)	0
Corrected QT prolongation	31 (41)	7 (9)	9 (24)	2 (5)
Reduced body weight	29 (38)	5 (7)	4 (11)	1 (3)
Elevated alanine aminotransferase	28 (37)	0	2 (5)	0
Elevated low-density lipoprotein	28 (37)	1 (1)	7 (19)	0
Reduced appetite	25 (33)	0	3 (8)	0
Oropharyngeal pain	23 (30)	0	2 (5)	0
Elevated aspartate transaminase	22 (29)	0	3 (8)	0
Elevated glutamyl transferase	21 (28)	3 (4)	2 (5)	1 (3)
Abdominal pain	19 (25)	0	3 (8)	0
Hyperuricemia	15 (20)	1 (1)	0	0
Oral mucositis	15 (20)	2 (3)	1 (3)	0
Hyperglycemia	14 (18)	0	3 (8)	0
Joint pain	14 (18)	2 (3)	1 (3)	0
Elevated conjugated bilirubin	13 (17)	0	5 (14)	0
Back pain	13 (17)	0	1 (3)	0
Hyperbilirubinemia	13 (17)	0	1 (3)	0
Elevated lipase	12 (16)	3 (4)	0	0
Cough	12 (16)	0	4 (11)	0
Headache	12 (16)	0	3 (8)	0

Note: Data are expressed in *N* (%).

(SAE) was 16% in the anlotinib group and 8% in the placebo group ($P = 0.378$). Twenty-three patients in the anlotinib group experienced bleeding events, all of which were grade 1 or 2.

One treatment-related death (1%) occurred. This patient had treatment interruption due to grade 1 QT interval prolongation and died of sudden myocardial infarction after stent implantation, which was deemed probably treatment related.

Quality of life

QoL was assessed by the questionnaire of EORTC QLQ-C30 and changes in QoL from the baseline to the end of treatment cycle 12 are shown in Supplementary Table S5. The scores at baseline were all comparable between evaluable patients in the two groups, except worse diarrhea symptoms in patients receiving anlotinib [mean (SD): anlotinib vs. placebo = 10.5 (17.4) vs. 5.4 (20.1), $P = 0.021$]. Patients receiving anlotinib experienced significant worsening from baseline in multiple domains, including physical functioning (cycles 6 to 12, $P < 0.05$), role functioning (cycles 4 to 12, $P < 0.05$), emotional functioning (cycles 4 and 12, $P < 0.05$), social functioning (cycles 6, 8, and 12, $P < 0.05$), global health status (cycle 6, $P = 0.049$), pain (cycles 4 to 12, $P < 0.05$), loss of appetite (cycles 6 to 10), diarrhea (cycles 6, 8, and 12, $P < 0.05$), and financial difficulties (cycles 4, 8, and 10, $P < 0.05$). However, significant difference in changes from baseline was only observed between the two groups in global health status (cycle 6, $P = 0.049$), fatigue (cycle 6, $P = 0.023$), nausea and vomiting (cycle 12, $P = 0.034$), pain (cycles 4 to 8, and 12, $P < 0.05$ or 0.001), loss of appetite (cycles 4 to 12, $P < 0.05$ or 0.001), diarrhea, (cycles 8 and 10, $P < 0.05$), and financial difficulties (cycles 6, 8, 10, and 12, $P < 0.05$). After 12 cycles of treatment, 83% patients in the anlotinib group and 51% patients in the placebo group were still evaluable. The scores of the two groups showed no significant difference in most items except pain [mean (SE) intergroup difference: anlotinib vs. placebo 7.7(3.3), $P = 0.018$] and diarrhea [mean (SE) intergroup difference: anlotinib vs. placebo 9.8(2.9), $P < 0.001$], which could be due to TRAEs such as palmar-plantar erythrodysesthesia syndrome and diarrhea. Patients in the anlotinib group showed no clinically meaningful changes (≥10 points) except deterioration of pain. Generally, anlotinib treatment had little influence on QoL.

Discussion

In this study, the median PFS for patients with locally advanced or metastatic RAIR-DTC reached 40.5 months in the anlotinib group with a 79% reduction in the risk of progression (HR = 0.21). In the Chinese 308 study and the REALITY study, the HR of lenvatinib and apatinib for PFS was 0.16 and 0.26, respectively (20, 21). The data for OS was still immature in the current trial, but the trend of OS benefit from anlotinib treatment had emerged, with an HR of 0.57 (95% CI, 0.29–1.12) and ECOG-PS was the only independent prognostic factor of OS. One important reason for lack of statistical difference of OS was the imbalance in subsequent treatments. Most patients (86%) in the placebo group received open-label anlotinib after disease progression, which could lead to a bias favorable to the placebo group. Indeed, when we adjusted the potential bias from crossover, anlotinib treatment achieved a clear OS benefit (HR = 0.36, 95% CI, 0.18–0.73). Patients with rapidly progressing disease appeared to have more survival benefits from anlotinib treatment.

In our study, although the data are immature, there was a trend toward improved OS in the unadjusted mITT analysis ($P = 0.098$). In the DECISION study, the trend of OS benefit was ambiguous. In the SELECT study, a nearly significant OS prolongation was observed after adjustment (HR = 0.62, 95% CI, 0.40–1.00, $P = 0.05$). In our study, we also observed that the benefit of anlotinib was more pronounced when using a method to adjust for bias due to cross-over; the observed HR decreased from 0.57 in the mITT analysis to 0.36 in the adjusted analysis. However, the adjusted OS analysis suggests what is intuitive, and the results are very preliminary and depend on unverified assumptions and must be interpreted cautiously. Furthermore, the cross-over of patients on the control arm to receive anlotinib at progression serves to attenuate the difference in OS between the two arms in the mITT analysis. This was observed in the SELECT trial and is observed in this study although the survival data are still immature. Recently, improved OS has also been reported for another antiangiogenesis TKI, apatinib (20). In a *post hoc* analysis, to attempt to correct potential bias from cross-over, as was done in the SELECT trial, the adjusted OS of the placebo group was also calculated, on the basis of a two-stage method derived from the RPSFT model. This method of adjustment assumes a "common treatment effect"—that the benefit of anlotinib among patients assigned to the control group who progress is not different than the benefit in patients initially randomized to receive anlotinib. It should be noted that the RPSFT model, although suggesting an anlotinib benefit in terms of OS, is prone to bias when the assumption of a "common treatment effect" is violated and this assumption will need to be validated once the mature survival data are available (19).

In our study, the median PFS of the placebo group reached 8.4 months and is longer than our assumption and that of the DECISION study (5.8 months). This discrepancy may reflect the fact that radiographic evidence of disease progression was not mandatory in our protocol. Another factor is that the study only included patients ages between 18 and 70 years. A subgroup analysis of the SELECT cohort showed a higher ORR (72% vs. 55%) and fewer toxicities in younger patients (<65 years vs. >65 years) and notably, patients age >65 years receiving lenvatinib had significantly longer OS compared with those receiving placebo (22). In our trial, multivariable analysis showed that anlotinib improved the PFS of patients regardless of age (<55 years vs. >55 years). In addition, our *post hoc* subgroup analysis showed that patients who had received early intervention appeared to gain more OS benefits, suggesting the importance of early intervention for patients with RAIR-DTC (23).

In accordance with the performance in the treatment of MTC, anlotinib showed an acceptable safety and tolerability profile in the context of long-term treatment (17). The incidence of common TRAEs for anlotinib seemed to be higher in this study compared with that in the study for MTC. For instance, the rate of any grade hypertension was 84% versus 47%, and the rate of ≥ grade 3 palmar-plantar erythrodysesthesia syndrome was 20% versus 13%. This may be attributed to the difference in the accumulated dose; the median duration of treatment was 24.4 months (IQR 13.3, 37.3) versus 14.0 months (IQR 6.7, 24.0) in the two studies. Similar observations were reported with lenvatinib for MTC and DTC. Furthermore, 8 patients (11%) receiving anlotinib permanently terminated treatment due to AEs versus 14% in patients receiving lenvatinib in the SELECT trial and 19% in patients receiving sorafenib in the DECISION trial (3, 4). Although the anlotinib discontinuation rate is not clearly superior to that of lenvatinib and sorafenib, patients in our trial had a median duration of treatment of 24.4 months, which is apparently longer than that of 13.8 and 10.6 months for lenvatinib and sorafenib, respectively. Most AEs were manageable and tolerable (20, 24–26). Despite a higher rate of AEs in the anlotinib group, there was no statistical difference in the incidence of treatment-related SAEs between the two groups (16% for anlotinib and 8% for placebo, $P = 0.378$), and only one case of treatment-related death occurred.

In the SELECT study and the 308 study, the incidence of treatment-related SAEs for lenvatinib was 30.3% and 22.3%, respectively, due to the lower body mass of Asians. Despite the long duration of treatment, anlotinib still maintained good tolerability. Only 34% patients in the anlotinib group required dose reduction. Good tolerability could be critical for achieving OS benefit. In the 308 study, 80.6% patients required dose adjustment, which may be partly due to the lower body mass of Asians. Despite a significant PFS benefit, the benefit for OS of lenvatinib is poor; the HR was only 0.84 (95% CI, 0.39–1.83). Overall, these findings suggest that anlotinib offers a safe and tolerable therapeutic option for patients with locally advanced or metastatic RAIR-DTC.

This study had several limitations. The study did not have a positive control arm because sorafenib and lenvatinib had not yet been approved for RAIR-DTC in China by SFDA at the start of the trial. Another limitation is the relatively high rate of consent withdrawal (21%) among patients receiving anlotinib (vs. 0% for placebo), which may affect the interpretation of the study data. Of note, 7 patients withdrew consent who had completed 12 cycles of anlotinib while 2 patients had completed 8 cycles of anlotinib, and 1 patient withdrew consent before completing 2 cycles of anlotinib. Moreover, a high percentage (86%) of patients in the placebo group received open-label anlotinib after disease progression. This made the interpretation of OS results more complicated. Currently, RAIR-DTC treatment remains challenging despite availability of MKI and RET and NTRK inhibitors. Lack of effective predictive biomarkers severely hampers implementation of molecularly stratified treatment of this patient population. Biomarker analysis should be incorporated into future trials.

In conclusion, this randomized controlled trial demonstrated that anlotinib could significantly extend the PFS of patients with locally advanced or metastatic RAIR-DTC. The toxicities are manageable and tolerable in long term treatment. On the basis of these data, Chinese FDA has approved anlotinib as a new choice for the treatment of RAIR-DTC.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

Y. Chi: Investigation, methodology, writing–original draft. **X. Zheng:** Investigation, methodology, writing–original draft. **Y. Zhang:** Investigation. **F. Shi:** Investigation. **Y. Cheng:** Investigation. **Z. Guo:** Investigation. **M. Ge:** Investigation. **J. Qin:** Investigation. **J. Zhang:** Investigation. **Z. Li:** Investigation. **X. Zhou:** Investigation. **R. Huang:** Investigation. **X. Chen:** Investigation. **H. Liu:** Investigation. **R. Cheng:** Investigation. **Z. Xu:** Investigation. **D. Li:** Investigation, methodology. **P. Tang:** Supervision, methodology, writing–review and editing. **M. Gao:** Supervision, methodology, project administration, writing–review and editing.

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Note

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