Donafenib in Locally Advanced/Metastatic Radioactive Iodine-Refractory Differentiated Thyroid Cancer: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Phase III Clinical Trial (DIRECTION)

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Abstract

Background

No available treatment existed in Chinese patients with progressive radioactive iodine–refractory differentiated thyroid cancer (RAIR-DTC) in terms of both affordability and safety upon the initiation of DIRECTION study. Donafenib is an oral tyrosine kinase inhibitor (TKI) with superior efficacy over sorafenib in hepatocellular carcinoma (HCC) phase III study. This study aimed to evaluate its antitumour activity and safety in Chinese RAIR-DTC patients.

Methods

The sequential phase II/III design as a whole protocol was approved by Center for Drug Evaluation (CDE) of the Chinese National Medical Products Administration (NMPA) by April 25, 2016. The phase II study was finished by March 2018. For the multicenter, double blind, placebo controlled, phase III study, 191 patients with locally advanced or metastatic RAIR-DTC progressed within the past 14 months were enrolled as per protocol design. Along with the approval sorafenib in China during the process of this study, sorafenib was accordingly introduced as an alternative to all the following patients for their option. Two interim analyses were planned. Patients were randomized in a ratio of 2:1 to donafenib (300 mg twice daily, \( n = 128 \)) or matched placebo (\( n = 63 \)). An open-label donafenib treatment period was allowed upon disease progression. The primary endpoint was progression-free survival (PFS) assessed by the independent review committee. Analysis was based on the intention-to-treat population (ITT). The second endpoint including (ORR), (OS), (DCR), safety, et al.

Results

Donafenib demonstrated prolonged median PFS over placebo (12.9 vs 6.4 months, hazard ratio (HR) 0.39, 95% confidence interval (CI) 0.25–0.61, \( p < 0.0001 \)) in Chinese RAIR-DTC patients either with prior TKIs (11.0 vs 3.7 months, HR 0.23, 95% CI 0.09–0.61) or not (18.3 vs 7.4 months, HR 0.45, 95% CI 0.27–0.73). Improved objective response rate (ORR) was observed in the donafenib group over placebo (23.3% vs 1.7%, \( p = 0.0002 \)). The most common grade \( \geq 3 \) treatment-related adverse events in the donafenib group included hypertension (13.3%) and HFS (12.5%). Of the donafenib group, 6.3% experienced discontinuation and 42.2% for dose reduction or interruption. The average daily dosage accounted for 87.0% of the initial dose, indicating the high adherence of patients to donafenib.

Conclusions

Donafenib meaningfully improved progression-free survival in patients with RAIR-DTC, particularly in those with prior TKIs. The high adherence of initial dose of donafenib as a result of the low occurrence of
grade 3 or above adverse events guaranteed its sustainable anti-tumour effect during treatment.

**Background**

The annual new cases of thyroid cancer have increased to 221,093 in China, accounting for more than one-third of the global annual new cases [1, 2]. According to Surveillance, Epidemiology and End Results (SEER) database, patients with thyroid cancer usually carry a favorable prognosis with the five-year survival rate of 98.3% in the United States, it is noteworthy the counterpart figure in China is only 84.3% [3, 4]. Differentiated thyroid cancer (DTC) accounts for the majority (over 90%) of thyroid cancer [5], most of which could achieve favorable response after standard treatment, including surgery, selective radioactive iodine (RAI) treatment and thyrotropin (TSH) suppression. More than one-third of high-risk DTC patients with locally advanced disease or distant metastasis eventually develop resistance to RAI therapy, which is identified as RAI-refractory DTC (RAIR-DTC) [6–8]. The 10-year survival rate of RAIR-DTC patients with distant metastasis is around 10%, rendering RAIR-DTC to a major clinical concern [8–10].

In the past decade, several signaling pathways and activating mutations have been identified to be involved in thyroid tumourigenesis, including the mitogen-activated protein kinase (MAPK) pathway and proangiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [11–13]. These findings have spurred the development of tyrosine kinase inhibitors (TKIs) to manage RAIR-DTC, including sorafenib and lenvatinib. Based on findings from DECISION and SELECT study, sorafenib and lenvatinib are recommended as the first-line therapy, with lenvatinib preferred [14, 15]. Of note, the high cost as well as the worrying safety profile of these TKIs become the major concern among Chinese patients, which prevent both of them from the clinical routine application.

With the above-mentioned considerations, protocols of exploratory phase II and phase III clinical trials of donafenib, a new domestic Chinese agent, were approved in 2016 in China, when there was no available TKI for Chinese RAIR-DTC patients due to the delayed approval of both sorafenib and lenvatinib in 2017 and 2020 respectively. Donafenib is explored as a modified form of sorafenib with a trideuterated N-methyl group, potentially enhancing molecular stability with an improved pharmacokinetic profile. It has been demonstrated to inhibit the activity of multiple receptor tyrosine kinases such as VEGF receptor, PDGF receptor, and various Raf kinases, thereby suppressing tumour cell proliferation and angiogenesis. In a phase III study for hepatocellular carcinoma (HCC), donafenib is superior to sorafenib in improving OS and has favorable safety in patients with advanced HCC. And in its phase II dose exploratory study for RAIR-DTC, 300 mg regimen (300 mg twice daily) appeared to be more clinically beneficial than 200 mg regimen (200 mg twice daily) in terms of prolonged PFS (14.98 vs. 9.44 months), favorable objective response rate (ORR, 13.3% vs 12.5%), and acceptable safety profile [16]. Based on the promising results the sequential phase III clinical trial was continued to assess PFS among patients with RAIR-DTC who received donafenib as compared with those who received the placebo.

**Methods**
Study design and participants

DIRECTION was a multicenter, randomized, double-blind, placebo-controlled, phase III trial, aimed to evaluate the efficacy and safety of donafenib for locally advanced or metastatic RAIR-DTC based on the best supportive treatment. The patients enrolled in this study met the following key criteria which were quite similar as DECISION study: 1) age 18 years or older; 2) locally advanced or metastatic RAIR-DTC (confirmed by histologic type: papillary, follicular, Hürthle cell, or poorly-differentiated cancer); 3) center-confirmed progression within the past 14 months according to Response Evaluation Criteria in Solid Tumours vision 1.1 (RECIST 1.1); and different from DECISION study patients who resisted to prior TKI treatments were allowed, but should be abstained for at least four weeks as a washout period; 4) at least one measurable lesion identified by CT or MRI according to RECIST 1.1; 5) expected survival time longer than 12 weeks; 6) adequate organ function and Eastern Cooperative Oncology Group (ECOG) score 0–2. RAIR-DTC was defined as at least one measurable lesion showed no RAI uptake on the scans for diagnosis or post $^{131}$I treatment, or at least one measurable lesion progressed within 14 months after the last $^{131}$I treatment with a dose of 3.7 ~ 7.4 GBq (100 ~ 200 mCi) despite the RAI avidity, or the cumulative $^{131}$I activity of at least 22 GBq (600 mCi) for RAI treatment.[17, 18] Identification for RAIR-DTC was based on the conditions of successful thyroid ablation, TSH > 30mIU/L and no interference of exogenous iodine (following low-iodine dietary restrictions and avoiding iodine contamination from IV contrast agents before RAI therapy).

The study was conducted in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Along with the approval sorafenib in China during the process of this study, sorafenib was accordingly introduced as an alternative to all the following patients for their option upon enrollment and unmasking. All patients provided written informed consent before screening. The study protocol and each revision were reviewed and approved by the ethics committee of all participating centers.

Randomization And Masking

Patients were randomized by the Central randomization system-interactive web response system (IWRS) in a ratio of 2:1 to receive donafenib (300 mg twice daily) or matching placebo in 28-day cycles. Study drugs were distributed to patients by investigators who were blind to treatment assignments through the exclusive drug number specified by IWRS. Randomization was stratified with distant metastasis (M0 vs M1) and TKI treatment history (yes vs no) using stratified blocked randomization method.

Study treatment and assessments

Safety was assessed every four weeks and efficacy evaluation according to RECIST 1.1 was conducted every eight weeks until progression or intolerable toxicity. The study drug interruption and dose reduction (up to four doses adjustment) were allowed when unacceptable adverse events (AEs) related to the study drug occurred. The dose reduction scheme is to sequentially reduce to 200 mg twice daily, 300 mg once
daily, 200 mg once daily and 200 mg once every other day. When grade 3 or above AEs occurred and didn't recover to grade 1 or less within two weeks after drug interruption, the test drug should be discontinued permanently.

Treatment regimen would be unmasked when disease progression was assessed and confirmed by IRC. As there was no available TKIs upon the approval of this trial, due to the ethnic concerns, a willingly entering to open-label period was allowed according to protocol when patients could continue to benefit determined by investigators. In open-label period, all patients in donafenib and placebo groups received donafenib until the second progression or intolerable toxicity.

Study End Points

The primary endpoint was PFS defined as the time from randomization to disease progression documented firstly and assessed by the independent review committee (IRC) or to death from any cause, whichever occurred first. Secondary endpoints included objective response rate (ORR, defined as the number of patients achieving an overall best response of complete response (CR) or partial response (PR) divided by the total number of patients), overall survival (OS, defined as time from randomization to death due to any cause), time to progression (TTP, defined as time from randomization to disease progression), disease control rate (DCR; defined as the number of patients achieving an overall best response of complete response (CR), partial response (PR) or stable disease (SD) for \( \geq 6 \) weeks \( \text{or} \ \geq 6 \) months in post-hoc analysis] divided by the total number of patients), the changes of thyroglobulin (Tg) and antithyroglobulin antibody (TgAb). Biochemical response defined as a decreased Tg level \( \geq 25\% \) and biochemical progression defined as a increased Tg level \( \geq 25\% \), Tg II and Anti-Tg by Roche Diagnostics GmbH were used to measure serum Tg and TgAb.[19] AEs were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical analysis

The primary efficacy analysis was based on the intention-to-treat (ITT) population, including all randomized patients. Objective response rate and disease control rate were analyzed based on the interim-ITT (iITT) population, which was a subset of ITT population and defined as patients with at least one post-baseline tumour assessment or who discontinued double-blind treatment due to any reason. The safety analysis set included all randomized patients who received at least one dose of study medication.

For the primary endpoint of PFS, it was estimated that 121 PFS events were required in the final analysis to achieve 80% power to detect a hazard ratio (HR) of 0.58 (assumed based on the results of donafenib phase II clinical trial in the locally advanced or metastatic RAIR-DTC and sorafenib DECISION trial) at a two-sided significance level \( (\alpha) \) of 0.05 with a 2:1 ratio of allocation to experimental group or control group. It was planned to perform the first and the second interim analyses when 55 (46% of total PFS events) and 81 PFS events (67% of total PFS events) were observed, respectively. A Lan-DeMets (O'Brien
(α & Fleming) a spending function was used to control the overall Type I error (false positive) probability. Assuming that PFS data maturity was 59%, around 204 patients were required (136 in the donafenib group and 68 in the placebo group). The first interim analysis and the second interim analysis were actually performed when 66 and 85 PFS events were observed, resulting in two-sided alpha of 0.0048 and 0.0135 being allocated to the two interim analyses respectively. An independent data monitoring committee (IDMC) consisting of two medical experts and one statistical expert was formed to review the interim analysis results and make recommendations on whether to stop the trial when the efficacy criteria of early termination was met.

The median PFS for each treatment group and the associated 95% confidence intervals were estimated using the Kaplan-Meier method. Kaplan-Meier graphs were plotted. A stratified log-rank test was used in the main PFS analysis to test if the difference between treatment groups were statistically significant. The HR with its 95% confidence intervals of PFS based on the comparison between treatment groups was estimated using a stratified Cox proportional hazards model. The stratification factor used for the analyses was history of prior tyrosine kinase inhibitors therapy (yes vs no). The randomization factor of distant metastasis was not considered as a stratification factor given that the category of M0 accounted for only 2.6% of the patients in the study. Subgroup analyses were also performed for pre-specified baseline variables to evaluate the consistency across different subgroups by means of unstratified Cox proportional hazards model. Differences in ORR and DCR were analyzed using the Cochran-Mantel-Haenszel test stratified by history of prior tyrosine kinase inhibitors therapy (yes vs no). The descriptive summary was provided for all safety parameters in the safety analysis set. Statistical analysis was performed using SAS version 9.4.

**Results**

From August 29, 2018, to February 28, 2021, a total of 191 patients in 34 clinical centers across China were randomized to donafenib \( (n = 128) \) or placebo \( (n = 63) \). The baseline characteristics of the patients were well balanced in these two groups (Table 1). At the time of data cutoff, the median follow-up time were 10.9 months (range, 0–30) in the donafenib group and 13.2 months (range, 1–29) in the placebo group, respectively. Totally, 92 patients (donafenib, 72 [56.3%]; placebo, 20 [31.7%]; Fig. 1) were continuing to receive blinded treatment, 72 patients (donafenib, 35 [27.3%]; placebo 37 [58.7%]) ended blinded treatment due to disease progression, and 3 patients (donafenib, 1 [0.8%]; placebo, 2 [3.2%]) ended blinded treatment due to death. Finally, 26 patients (20.3%) with donafenib and 39 patients (61.9%) with placebo received open-label donafenib.
Table 1
Baseline characteristics in the intention-to-treat population

<table>
<thead>
<tr>
<th></th>
<th>Donafenib (n = 128)</th>
<th>Placebo (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59 (31–76)</td>
<td>60 (27–74)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>30 (23.4%)</td>
<td>22 (34.9%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>57 (44.5%)</td>
<td>27 (42.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>71 (55.5%)</td>
<td>36 (57.1%)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>76 (59.4%)</td>
<td>40 (63.5%)</td>
</tr>
<tr>
<td>1</td>
<td>49 (38.3%)</td>
<td>23 (36.5%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (2.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Time from initial diagnosis, month</td>
<td>68.1 (3.4–350.0)</td>
<td>53.5 (9.4–269.4)</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>104 (81.3%)</td>
<td>45 (71.4%)</td>
</tr>
<tr>
<td>Follicular</td>
<td>21 (16.4%)</td>
<td>17 (27.0%)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>2 (1.6%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Distant metastasis†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>3 (2.3%)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>M1</td>
<td>125 (97.7%)</td>
<td>61 (96.8%)</td>
</tr>
<tr>
<td>Metastatic lesions†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>3 (2.3%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>72 (56.3%)</td>
<td>30 (47.6%)</td>
</tr>
<tr>
<td>Lung</td>
<td>121 (94.5%)</td>
<td>60 (95.2%)</td>
</tr>
<tr>
<td>Bone</td>
<td>36 (28.1%)</td>
<td>8 (12.7%)</td>
</tr>
<tr>
<td>Liver</td>
<td>6 (4.7%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (18.0%)</td>
<td>10 (15.9%)</td>
</tr>
</tbody>
</table>

Data are n (%) or median (range). ECOG = Eastern Cooperative Oncology Group. M = metastasis. TKI = tyrosine kinase inhibitor. †per investigator assessment.
Donafenib ($n = 128$) | Placebo ($n = 63$)
---|---
Prior therapies | 
Chemotherapy | 3 (2.3%) | 2 (3.2%) |
Radiotherapy (local lesion or bone/brain metastasis) | 17 (13.3%) | 8 (12.7%) |
Interventional therapy | 4 (3.1%) | 0 |
TKI therapy | 24 (18.8%) | 11 (17.5%) |
Cumulative activity of radioiodine, mCi | 400 (100–1780) | 400 (114–1400) |
$< 600$ mCi | 92 (71.9%) | 41 (65.1%) |
$\geq 600$ mCi | 36 (28.1%) | 22 (34.9%) |

Data are $n$ (%) or median (range). ECOG = Eastern Cooperative Oncology Group. M = metastasis. TKI = tyrosine kinase inhibitor. †per investigator assessment.

### Efficacy

The primary endpoint of PFS was met at the time of analysis (February 2021), showing significant improvement in PFS for donafenib compared with placebo (median 12.9 vs 6.4 months, HR 0.39; 95% CI, 0.25–0.61; $p < 0.0001$; Fig. 2A), with a 61% reduction in the risk of progression or death during the double-blind period. The 12-month PFS rates were 54.1% (95% CI 42.4–64.5) and 26.1% (95% CI 14.1–39.9) in donafenib and placebo group, respectively.

In the prespecified subgroups analysis, all participants tended to benefit from donafenib in PFS, irrespective of clinicopathological features (i.e., subgroups defined according to age, gender, histologic type, performance status, with prior TKI treatment or not, baseline metastatic status, cumulative RAI dose; Fig. 3). Totally 18.3% (35/191; donafenib group, 18.8%; placebo group, 17.5%) patients received prior TKI treatment (supplementary table S3), the corresponding data was 11.0 months (donafenib) vs 3.7 months (placebo) (HR 0.23, 95% CI 0.09–0.61). While for TKI-naïve subgroup the median PFS was 18.3 months (donafenib) vs 7.4 months (placebo) (HR 0.45, 95% CI 0.27–0.73);

Donafenib was associated with improved ORR (based on iITT all confirmed partial response, 23.3% [28/120] over placebo (1.7% [1/58]; $p = 0.0002$; supplementary table S2). The median time to confirmed objective response for donafenib was 1.84 months (95% CI 1.81–2.83). The median duration of response for patients with a PR to donafenib was 16.53 months (95% CI 10.97-NE). Higher incidence of tumour shrinkage was observed in the donafenib over placebo (Fig. 2B).

DCR (PR plus SD for $\geq$ 6 months from randomization; post-hoc analysis) was 52.5% (63/120) for patients with donafenib while 29.3% (17/58) for patients with placebo, respectively ($p = 0.0032$; supplementary table S2). The median TTP was 12.9 months with donafenib and 7.3 months with
placebo (HR 0.381, 95% CI 0.24–0.60; \( p < 0.0001 \)). Totally 24 patients (donafenib, 13 [10.2%]; placebo, 11 [17.5%]) died before the data cutoff. As few occurrences of OS events observed thus the median OS was not yet reached, this may owe to the cross-over design and more than 60% patients from placebo crossed over to donafenib who showed a continuing PFS from the cross-over donafenib treatment. (Fig. 2C). The 6-month, 12-month and 18-month survival rates in the donafenib group were 100%, 91.8%, and 88.3%, while 98.3%, and 89.0% and 73.5% in the placebo group, respectively.

Median serum Tg dropped from baseline rapidly in the first eight weeks and remained at a low level over treatment in the donafenib group, but in the placebo group the median serum Tg increased from the baseline and remained upward. (Fig. 2E) Early in cycle two, biochemical response was observed in 74.1% of patients in the donafenib group and 9.3% in the placebo group, while biochemical progression was observed in 4.7% of patients with donafenib and 34.9% of patients with placebo (supplementary figure S1).

The median duration of treatment was 233.5 days (range, 4–910) among patients who received donafenib, and 176.0 days (range, 21–872) among patients who received placebo. The average daily dose was 522 mg/day in the donafenib group, accounting for 87.0% of the initial intensity (600 mg/day). In double-blind period, among patients receiving donafenib 85(66.41%) maintained the initial dose of 600mg/day, while 29(22.66%), 9(7.03%) and 5(3.91%) modified to 400mg, 300mg, 200mg/day, respectively. (Fig. 2D)

### Exposure and safety

Treatment related adverse events (TRAEs) occurred in 99.2% (127/128) of patients receiving donafenib and in 44.4% (28/63) of patients receiving placebo during the double-blind period (Table 2). Overall, TRAEs of grade 3 or higher occurred in 43.8% of the patients in the donafenib group. The most frequent TRAEs in the donafenib group were HFS \(( n = 108, 84.4\%)\), alopecia \(( n = 86, 67.2\%)\) and diarrhea \(( n = 81, 63.3\%; \text{Table 2})\). The TRAEs of grade \(\geq 3\) (with incidence of >5%) included hypertension \(( n = 17, 13.3\%)\) and HFS \(( n = 16, 12.5\%)\). Serious adverse events occurred in 22.7% (29/128) of patients with donafenib, of which 10 cases were treatment related. Correspondingly, serious adverse events occurred in 19.0% (12/63) of patients with the placebo. Serious adverse events that occurred in 2% or more of patients with donafenib were lung inflammation (3.1% [4/128]) and abnormal liver function (2.3% [3/128]). Two treatment-emergent deaths occurred in the donafenib group and two in the placebo group, which were all attributable to underlying disease. (supplementary table S4, S5)
Table 2
Summary of Treatment related adverse events (TRAEs) in double-blind treatment period

<table>
<thead>
<tr>
<th></th>
<th>Donafenib (n = 128)</th>
<th></th>
<th>Placebo (n = 63)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥ 3</td>
<td>Any Grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Any TRAEs, n (%)</td>
<td>127 (99.2%)</td>
<td>56 (43.8%)</td>
<td>28 (44.4%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>AESI*</td>
<td>89 (69.5%)</td>
<td>11 (17.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose interruption or reduction</td>
<td>54 (42.2%)</td>
<td>1 (1.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation of treatment</td>
<td>8 (6.3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAEs</td>
<td>10 (7.8%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAEs in ≥ 10% of patients, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>108 (84.4%)</td>
<td>16 (12.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>86 (67.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>81 (63.3%)</td>
<td>4 (3.1%)</td>
<td>3 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (46.9%)</td>
<td>17 (13.3%)</td>
<td>2 (3.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>49 (38.3%)</td>
<td>2 (1.6%)</td>
<td>6 (9.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>44 (34.4%)</td>
<td>2 (1.6%)</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>33 (25.8%)</td>
<td>2 (1.6%)</td>
<td>3 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>29 (22.7%)</td>
<td>4 (3.1%)</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>23 (18.0%)</td>
<td>1 (0.8%)</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>23 (18.0%)</td>
<td>1 (0.8%)</td>
<td>2 (3.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>19 (14.8%)</td>
<td>1 (0.8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>18 (14.1%)</td>
<td>2 (1.6%)</td>
<td>3 (4.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>17 (13.3%)</td>
<td>2 (1.6%)</td>
<td>1 (1.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>15 (11.7%)</td>
<td>4 (3.1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>14 (10.9%)</td>
<td>1 (0.8%)</td>
<td>2 (3.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (10.9%)</td>
<td>1 (0.8%)</td>
<td>4 (6.3%)</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>13 (10.2%)</td>
<td>2 (1.6%)</td>
<td>3 (4.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* AESI: Adverse events of special interest, including hypertension, proteinuria, QT interval prolongation and hemoptysis.
TRAEs leading to dose reduction or interruption occurred in 42.2% (54/128) of patients with donafenib and 1.6% (1/63) of patients with placebo. The most common reasons for donafenib dose reduction or interruption were HFS (16/128, 12.5%), hypertension (14/128, 10.9%) and diarrhea (5/128, 3.9%), and discontinuation of treatment occurred in 6.3% (8/128) of patients with donafenib. The most frequent causes of donafenib dose discontinuation were abnormal liver function (3/128, 2.3%) and rash (2/128, 1.6%).

**Discussion**

**Efficacy**

In this study which enrolled the largest Chinese RAIR-DTC cohort, donafenib demonstrated clinical benefit with prolonged PFS over placebo, reduced disease progression (PD) or death by 61.1% over placebo (PFS 12.9 vs. 6.4 months, HR 0.389); the ORR for donafenib was 23.3%. Of note, although DECISION study enrolled Chinese RAIR-DTC patients, but no patients with prior TKIs were included according to its protocol, while here in DERECTION study, around 1/5 patients with prior TKIs including sorafenib, lenvatinib, apatinib, anlotinib, et al. showed continue clinical benefit from donafenib (HR = 0.227). Even if the amount of these patients were relatively limited, but the efficacy was promising enough to demonstrate that donafenib could be an option for patients with prior TKIs. Donafenib also showed longer overall survival trend with 14.8% increase of 18-month survival rates (88.3% vs. 73.5%).

**Biochemical response**

Tg is a sensitive and convenient biochemical responsive marker for DTC after total thyroidectomy and RAI therapy. In this study, biochemical response can be observed in the donafenib group within the early 2 cycles and remained throughout the treatment, suggesting a rapid and long-lasting biochemical response of donafenib. Considering the early and rapid biochemical response, we proposed that the commonly used imaging-based evaluation, which is usually conducted at an interval of 8 to 12 weeks after the initiation of TKI, might miss the probable early therapeutic response in RAIR-DTC but may be reflected by Tg as a sensitive biochemical marker.

**Safety**

In the current study, the treatment-related adverse events spectrum was generally consistent with the known donafenib safety profile reported in the phase II trial for RAIR-DTC and phase III trial for hepatocellular cancer [16, 20]. Donafenib also exhibited promising safety particularly in the 13.3%, 1.6% and 0 occurrence rate of ≥ grade 3 hypertension, proteinuria and death, respectively. The favorable safety profile probably lies in its refined pharmacokinetic feature, thus allowed the high adherence of average daily dose to its initial dose (87.0%), and added promise to its sustainable antitumour effect with 14.8% increase of 18-month OS rate.

**Limitation**
Placebo was used as a control rather than sorafenib or lenvatinib since they were approved as a fixed phase II/III design in 2016 when there was no available TKIs indicated for RAIR-DTC patients in China, all patients with placebo were allowed to cross-over to open-label donafenib upon disease progression for the ethical concern. And the patients were accordingly informed about the available TKIs along with the following approval of sorafenib and lenvatinib during enrollment. Luckily, result from the phase III study for hepatocellular carcinoma (HCC), showed donafenib is superior to sorafenib in improving OS and has favorable safety in patients with advanced HCC, the superiority over sorafenib in patients with RAIR-DTC need to be confirmed in head-to-head comparative real-world study. This is an interim analysis, and the median OS is not mature, the data would be updated to provide long-term survival benefit evidence.

**Conclusion**

Donafenib significantly improved progression-free survival in patients with RAIR-DTC, particularly in those with prior TKI. The low occurrence of adverse events ≥ grade 3 allowed the high adherence of initial dose of donafenib and guaranteed its sustainable antitumour effect during treatment.

**Declarations**

**Acknowledgements**

This study was funded by Zelgen. We thank all the patients and their families, the dedication from all the investigators, the teams who participated in this trial, and Prof Shukui Qin, MD (PLA Cancer Centre, Nanjing Jinling Hospital, Nanjing, China) for giving professional advice on protocol designing. We also thank Zhuanzhuan Mu, Xin Zhang (Department of Nuclear Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College (PUMC) Hospital, Chinese Academy of Medical Sciences & PUMC, Beijing, China), and YingJie Zhang (Shandong Cancer Hospital and Institute & Shandong First Medical University and Shandong Academy of Medical Science, Jinan, China) who provided medical writing support (funded by Zelgen).

**Authors’ contributions**

YS Lin and LQ Wu designed the study. H Yang, YS Lin, F Shi, AM Yang, XM Han, B Liu, ZY Li, QH Ji, LJ Tang, ZY Deng, Y Ding, W Fu, XH Xie, LF Li, XH He, ZW Lv, QJ Ma, Z Shen, ZM Guo, ZD Chen, YL Cui, JTan, ZR Gao, SH Jing, KY Lu, XY Luo, Y Zhang, Y Fang, ZD Li, YZ Cheng, ST Lei, X Luan, G Chen, and GH Wang enrolled participants and collected the data. LL Liu provided statistical analyses. All authors were involved in the data interpretation, manuscript development, and approval for publication.

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Academy of Medical Sciences (No. 2019XK320009); and Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS) (No. 2020-I2M-2-003).

**Ethics approval and consent to participate**

The study was formally approved by the Ethical Committee of Peking Union medical College Hospital. The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice. The corresponding local ethics committee of each participating institution has approved the DIRECTION study. DIRECTION has been registered at www.clinicaltrials.gov with the identifier NCT03602495 and at www.chictr.org.cn with the identifier CTR20180191. The anonymized data that do not contain any personally identifiable information from any sources implies that the informed consent is not applicable.

**Competing interests**

LQ Wu and LL Liu are employees of Zelgen. All authors have declared no conflicts of interest.

**References**


**Figures**
Figure 1

Trial profile
Figure 2

Tumour response assessed by IRC according to RECIST v1.1

(A) Kaplan-Meier analysis of PFS. (B) Waterfall plot for maximum percentage tumour reduction from baseline in target lesions for individual patients. (C) Kaplan-Meier analysis of overall survival. (D) Duration of treatment with different dose in each patient (donafenib group; post-hoc). (E) Biochemical response in terms of thyroglobulin change.

CI=confidence interval. HR=hazard ratio. RECIST= Response Evaluation Criteria in Solid Tumours. Tumour response was assessed and confirmed by independent review committee. Only patients with at least one baseline and post-baseline assessment are shown. Negative values refer to maximum percentage reduction and positive values to the minimum increase from baseline in sum of diameters of target lesions.
Figure 3

Forest plot of HRs for PFS subgroup analyses assessed by IRC according to RECIST v1.1 CI=confidence interval. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. IRC= independent review committee. RAI=radioactive iodine. RECIST= Response Evaluation Criteria in Solid Tumours. TKI=tyrosine kinase inhibitor.

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<th>Supplementary Files</th>
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- SupplementaryAppendix.docx