BMJ Open

Donafenib as neoadjuvant therapy in locally advanced thyroid cancer: protocol for the DONATHYCA phase II prospective single-arm trial in China

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To cite: Yu J, Liu H, Wu Y. Donafenib as neoadjuvant therapy in locally advanced thyroid cancer: protocol for the DONATHYCA phase II prospective single-arm trial in China. *BMJ Open* 2024;**14**:e081090. doi:10.1136/bmjopen-2023-081090

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-081090).

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Received 18 October 2023
Accepted 25 March 2024

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ABSTRACT

Introduction The invasion of important structures in locally advanced thyroid cancer (LATC) hinders radical resection, increases the risk of recurrence and even prevents surgery. Creating the opportunity for radical operation in patients with LATC is critical for improving their prognosis. Multitarget tyrosine kinase inhibitors were used as neoadjuvant therapy in several studies. Donafenib produced survival benefits over placebo in Chinese patients with radioiodine-refractory differentiated thyroid cancer in a recent study, but its efficacy in the neoadjuvant setting remains unknown. This study thus aims to assess the efficacy and safety of donafenib as neoadjuvant therapy in LATC.

Methods and analysis DONATHYCA is a prospective, exploratory, single-arm phase II study evaluating the efficacy and safety of donafenib as neoadjuvant therapy in patients with LATC. 13 patients will be enrolled. The primary endpoint is the objective response rate as per Response Evaluation Criteria in Solid Tumours V.1.1. The secondary objectives include progression-free survival, the duration of response, the disease control rate, the R0/R1 resection rate, quality of life and toxicity during treatment according to Common Terminology Criteria for Adverse Events V.4.0. Patients will receive donafenib 300 mg two times a day continuously in a 21-day treatment cycle for six cycles.

Ethics and dissemination This study was approved by the Ethics Committee of Fujian Cancer Hospital (K2023-144-02) on 27 July 2023 and registered in the China Clinical Trial Registry on 20 September 2023. The results of the study will be presented at academic conferences and published in scientific publications.

Trial registration number ChiCTR2300075973

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This prospective study will be conducted in a single centre.
⇒ The endpoints of this trial were objective indicators.
⇒ The relatively small sample may increase the risk of error II.

INTRODUCTION

Thyroid cancer is a common endocrine malignancy with an increasing annual incidence globally.[1] Approximately 586 000 new cases of thyroid cancer were reported globally in 2018, ranking it ninth among all cancers.[2] Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are collectively called differentiated thyroid cancers (DTCs), which account for approximately 95% of thyroid cancers and generally carry a generally favourable prognosis and a low associated mortality rate.[3] However, the invasion of important structures (trachea, oesophagus, larynx, anterior vertebral fascia, brachial plexus and the common carotid artery) increases the difficulty of radical resection and the risk of recurrence and potentially prevents surgery.[4] Therefore, creating the opportunity for radical operation in patients with locally advanced thyroid cancer (LATC) is critical for improving their prognosis.

Neoadjuvant treatment is a widely accepted therapeutic option for patients with cancer, and it has been proven to downstage cancer, increase the likelihood of radical resection and improve survival.[5–7] However, neoadjuvant therapy remains in the exploratory stages for thyroid cancer.[8 9] At present, multitarget tyrosine kinase inhibitors are the main drugs for the treatment of advanced iodine-resistant differentiated thyroid cancer, and of these drugs, lenvatinib and sorafenib have been recommended in China. Neoadjuvant therapy with these two drugs in LATC has also been reported.[10–12] Tsuboi *et al* were the first to report a case of locally advanced PTC treated with lenvatinib neoadjuvant therapy.[10] The patient initially presented with tumour invasion of the cervical oesophagus and trachea. After 18 weeks of treatment with lenvatinib, the primary tumour and cervical lymph nodes had shrunk by 84.3% and 56.0%, respectively, and the patient subsequently underwent radical resection. Similar

situations were also reported by Iwasaki *et al* and Stewart *et al*.[11 13] In addition, Nava *et al* reported cases of neoadjuvant therapy with sorafenib. The tumour had shrunk by 70% after 6 months of therapy, and radionuclide therapy was further performed after complete resection.[14]

Related clinical trials on neoadjuvant target therapy (NTT) in LATC were recently reported. A phase II clinical trial assessing the efficacy and safety of anlotinib as NTT enrolled a total of 13 patients, with 12 cases being differentiated thyroid cancer and only 1 case being poorly differentiated thyroid cancer. The median number of cycles was 3.5, and the objective response rate (ORR) and R0/R1 resection rate were 76.9% and 61.5%, respectively. The treatment had an acceptable adverse event profile.[15] Another study exploring the efficacy and safety of surufatinib combined with anti-PD-1 (programmed death 1) antibody toripalimab in NTT, enrolling only 10 patients with differentiated thyroid cancer as the target population, showed a 60% (95% CI: 26% to 88%) objective response rate and a 90% R0/R1 resection rate.[16] Moreover, a recent study was recruiting which was aimed to examine the efficacy and safety of lenvatinib prior to thyroidectomy, with the goal of achieving more favourable surgical outcomes.[17] These studies suggest that patients with differentiated thyroid cancer can achieve favourable therapeutic effects when receiving tyrosine kinase inhibitor (TKI) or TKI combined with immunotherapy as neoadjuvant treatment.

Donafenib, an oral small-molecule multikinase inhibitor, is a deuterium derivative of sorafenib that is under development by Zelgen Biopharmaceuticals (Zelgen, Suzhou, China) for the treatment of various cancers, including hepatocellular carcinoma, colorectal cancer and thyroid cancer.[18] It exerts its antineoplastic effect via two mechanisms: directly by inhibiting serine/threonine kinase, thereby blocking the Raf/MEK/ERK signalling pathway, and indirectly by inhibiting VEGFR and PDGFR, thereby blocking tumour angiogenesis.[18] The efficacy and safety of donafenib have been demonstrated in several tumours.[10 19] A randomised, open-label phase II trial (NCT02870569) recorded tumour shrinkage in 58.1% of patients who received donafenib 200 or 300 mg two times a day for 24 weeks for locally advanced or metastatic radioiodine-refractory (RAIR)-DTC.[20] Moreover, donafenib prolonged median progression-free survival (PFS) versus placebo (12.9 months vs 6.4 months, p<0.001) in Chinese patients with RAIR-DTC.[21] However, its efficacy in patients with LATC remains unknown. Given that data on neoadjuvant therapy in LATC are extremely limited, this study was planned to investigate the efficacy and safety of donafenib and identify the best possible options for neoadjuvant therapy in LATC.

According to the eligibility criteria, all enrolled cases would be those who are difficult to perform R0 resection, but still have the opportunity to benefit from radical surgery. Even though all patients would receive fine needle aspiration (FNA) before treatment, it is difficult to diagnose as poor differentiate thyroid cancer (PDTC) or anaplastic thyroid cancer by FNA. Considering the low incidence of advanced thyroid cancer (ATC) and PDTC and the relatively small sample in the phase II study, we did not enrol PDTC and ATC in the study design. Current studies revealed that various pathological subtypes of thyroid cancer have different responses to drugs.[22] The inclusion of multiple pathological types in a small sample size II phase study does not reflect the efficiency of the TKI regimen. A multicentre phase III study to explore patients with ATC and PDTC may be a more appropriate choice.

Hence, we propose the use of donafenib to achieve a relatively high ORR and R0/R1 resection rate in this study. This trial is designed to increase the available novel neoadjuvant therapies for patients with LATC. Our ultimate goal is to improve survival outcomes for patients. However, sample size limitations are inevitable in a phase II trial, and we acknowledge that there are risks of underpowering and type II errors.[23] Larger trials of the efficacy and clinical application of donafenib will be necessary if DONATHYCA produces positive results. We hope that this initial trial will provide sufficient evidence to support and inform future such trials.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Method and analysis

This protocol of the DONATHYCA trial is drafted according to the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[24]

Study design

DONATHYCA is a prospective, exploratory, single-arm, phase II study designed to evaluate the efficacy and safety of donafenib as a neoadjuvant treatment for patients with LATC. The study is expected to begin in October 2023 and end in September 2025. Figure 1 presents the schedule of enrolment, interventions and assessments.

In this study, we plan to enrol patients with LATC that were deemed unresectable or difficult to treat via radical resection. All patients will receive donafenib 300 mg two times a day and continuously in a 21-day treatment cycle until disease progression, intolerable toxicity or the patient's decision to withdraw from the study. A maximum of six cycles will be completed. Donafenib will be discontinued 1 week before surgery. A detailed evaluation of potential patients will be conducted by a trained clinical research coordinator. All related data will be recorded in the electronic case report form (eCRF).

Patient and public involvement

None.

Primary endpoint

The primary endpoint is the ORR per Response Evaluation Criteria in Solid Tumours (RECIST) V.1.1 to evaluate the efficacy of donafenib as neoadjuvant therapy in patients with LATC.

Time	Screening period	Treatment Period		Operation	Postoperative follow-up	
		Cycle 1	The following cycle	Discontinuation for a week preoperation	Safety	Effectiveness
	Within 28 days	C1D1	C2D1、C3D1……C6D1		Within 30 (± 7) days after the last dose	
		± 3 days	± 3 days			
Informed consent[1]	×					
Demographic information	×					
History of disease and treatment	×					
Confirmation of the inclusion / exclusion criteria	×					
Physical examination[2]	×	×	×	×	×	
Vital sign	×	×	×	×	×	
ECOG PS Score[3]	×	×	×	×		
Blood routine/biochemistry, urine routine, and coagulation function[4]	×	×	×	×	×	
Pregnancy tests (if applicable)[5]	×		×	×	×	
ECG[4]	×	×	×	×	×	
Cardiac ultrasound	×					
thyroid function[6]	×		×	×	×	
Neck / chest CT / MRI examination[7-8]	×	Once in every two cycles (6 weeks) ± 7 days				×
Release / recycle donafenib[9]		×	×	×		
Release / recycle donafenib medication logs[10]		×	×	×		
Concomitant medication / concomitant therapy[11]	----------→					
Adverse event[12]	----------→					
survival status[13]			×	×	×	×

Figure 1 The evaluation schedule of enrolment, interventions and assessments in the DONATHYCA trial. C1D1, cycle 1 day 1; ECOG, Eastern Cooperative Oncology Group; PS, performance status. Remarks: (1)The informed consent form (ICF) signed by the subject must be obtained before the commencement of all study procedures specified in this study. (2) Physical examination included measurement of height and weight, and examination of all organ systems. Height is only performed at visit 1, not measured for other visits. (3) ECOG PS scale, if performed within 3 days before the first dose, does not need to repeat the collection on day 1 of cycle 1. (4) The safety examination during the treatment period must be completed before each cycle, and the blood collection cannot be earlier than 3 days before the medication, and the results must be determined by the investigator to meet the criteria for continued medication before initiation; if the blood routine, blood biochemistry, urine routine, coagulation and ECG examination during the screening period are performed within 3 days before the first dose, the corresponding examination on the first day of cycle 1 cannot be done and the examination results during the screening period can be used as baseline data. (5) Blood pregnancy test was only in the screening period, end of treatment or early withdrawal, urine pregnancy test during study treatment and safety follow-up period after the last administration and blood test pregnancy if the result is positive. (6) Thyroid function test: serum FT3, FT4, TSH, Tg and TgAb, within 28 days before medication, on day 1 of cycle 2, once every two cycles and at the end of the study. (7) Imaging examination: including neck and chest CT or MRI. Baseline tumour assessment during the screening period can be extended to 4 weeks before treatment; CT/MRI scans obtained before informed consent can be used for screening tumour assessment; bone scan is clearly or clinically suspected. The imaging examination during the treatment period should be evaluated with the same assessment method as at baseline under the same conditions as the baseline examination (scan thickness, contrast medium use), bone scan for bone progression or complete response confirmation (patients with bone metastasis at baseline), if new lesions are suspected. For first disease progression per Response Evaluation Criteria in Solid Tumours V.1.1, confirmation is required after 4–6 weeks (except for rapid progression, significant clinical progression); the window allowed by the imaging schedule is ±7 days. Unscheduled imaging may be performed when disease progression (eg, deterioration of symptoms) is suspected. (8) If patients acquired R0/R1 resection, the patient will be individualised evaluation according to the actual situation. In case of inoperable or non-R0/R1 resection, within 4 weeks before the end of the trial, imaging evaluation shall be performed at the end of the treatment. Meanwhile, efficacy is evaluated every 3 months after the end of the trial until confirmed disease progression or new anti-tumour therapy is documented. (9) In C1D1, according to the determined dose of the subject, the corresponding number of drugs was distributed to the subject. After day 1 of each cycle, the number of drugs required for this cycle will be issued and the remaining drugs and empty boxes from the previous cycle will be recovered. (10) The first cycle donafenib medication log will only be issued to the subject at C1D1 and will be recovered at the visit of the next cycle day 1. Subject medication log for this cycle will be issued on day 1 of each cycle and recovered at the next cycle day 1 visit; end of treatment/early withdrawal visit medication log. (11) From 28 days prior to enrolment, all drugs/treatments the subject received must be recorded in the case report form, including generic name and dose, frequency, route, reason for the drug/treatment and start and end date. If there are new changes in drug therapy, they must be constantly updated. (12) Adverse events were collected from the start of the ICF until 30 days (±7 days) after the last dose or initiation of new anti-tumour therapy, whichever occurred first. Pre-existing adverse signs, symptoms or medical conditions at the time of signing the informed consent should be recorded as medical history. Survival follow-up: After discontinuation/completion of trial treatment, survival status and subsequent anti-tumour treatment can be collected by clinical follow-up or telephone call every 6–12 months until death.

Secondary objectives

The secondary endpoints are as follows:

- R0/R1 resection rate defined as the proportion of patients who undergo radical resection or exhibit residual disease among all patients undergoing surgery.
- PFS defined as the time between treatment initiation and progression.
- Duration of response defined as the time from the first evaluation of complete response (CR) or partial response (PR) to the first evaluation of progressive disease or death from any cause.
- Disease control rate defined as proportion of patients with disease control (CR or PR) or stable disease for a certain period.
- Recurrence-free survival defined as the time from complete remission to recurrence or the end of follow-up after anti-neoplastic therapy.
- Drug-related toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) V.4.0.

Eligibility criteria

The most specific eligibility criteria were included in the online supplemental materials. The main inclusion criteria of patients included: Willing to follow the protocol during the study period; age of 14–80 years; confirmation of DTC, including PTC and FTC, by FNA; patient with cT3–4aN+M0 (the American Joint Committee on Cancer (AJCC) tumour clinical stage) and an estimation that radical resection is difficult to achieve; no prior antineoplastic treatment; at least one measurable target lesion (longest diameter ≥10 mm or shortest diameter of lymph nodes ≥15 mm) in accordance with RECIST V.1.1; Eastern Cooperative Oncology Group performance status 0–1; no severe concomitant disease and an expected survival time exceeding 3 months; sufficient physical status and organ functions to permit major surgery; baseline routine blood test and biochemical indices meeting the prespecified criteria (haemoglobin ≥90 g/L; absolute neutrophil count ≥1.5 × 10^9/L; platelets ≥100 × 10^9/L; alanine aminotransferase and aspartate aminotransferase ≤2.5 × the upper limit of normal (ULN); alkaline phosphatase ≤2.5 × ULN; serum total bilirubin <1.5 × ULN; serum creatinine <1 × ULN; serum albumin ≥30 g/L).

The main exclusion criteria for this study are as follows: Pathology of medullary or anaplastic thyroid cancer; receipt of local ablation and radioiodine therapy within 3 months prior to inclusion; prior receipt of drugs inhibiting VEGF, including, but not limited to, anlotinib, apatinib, bevacizumab and lenvatinib; history of psychiatric illness; history of allergy to donafenib or targeted drugs or active bleeding or abnormal coagulation; history of gastrointestinal perforation or bleeding in the past 4 weeks and thrombosis or thromboembolism events or severe cardiopulmonary diseases within the past 6 months; pregnancy women; inability to follow following the study protocol and follow-up scheme.

The termination criteria are as follows: Subjects are required to withdraw from the clinical study; progressive disease was identified according to RECIST V.1.1; toxicities were intolerable even after dose adjustment; deterioration of the health status to an extent that precludes further participation in the study; radical surgery is not possible after six cycles of therapy; patients refuse surgery after neoadjuvant therapy or are lost to follow-up.

Study site

This study will be conducted in the Department of Head and Neck Surgery, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital.

Donafenib

Subjects in this trial will receive donafenib 300 mg two times a day continuously in each 21-day treatment cycle. Treatment will be stopped if any of the following occurs: (1) six cycles are completed; (2) the subjects exhibit intolerable toxicity that is not relieved even after dose adjustment or treatment interruption; (3) disease progression is confirmed by CT and ultrasonography; and (4) patients refuse continuous treatment.

During the treatment, a maximum of three dose adjustments will be allowed for the subjects because of severe adverse events related to donafenib according to CTCAE V.4.0. The scheme of adjustment is presented in online supplemental table 1.

Drug supply

Donafenib will be provided by the Sponsor (Suzhou Zelgen Biopharmaceutical).

Calculation of the number of patients

Assuming a null ORR of 5% for placebo, an ORR of 20% for donafenib, a one-sided α of 0.025 and β of 0.20, 11 patients are required. Considering a dropout rate of 15%, the target enrolment is 13 patients. If treatment efficacy is confirmed in at least three patients, the results will be regarded as positive. Even though the sample size was calculated according to the relevant statistical parameters. The relatively small sample size could decrease the reliability and validity of the research results, increase the type II error.[25] A study with a large sample may be performed based on the results of this study.

Statistical analysis plan

Qualitative data will be presented as absolute frequencies, relative frequencies, 95% CIs and percentages of missing data. Quantitative data will be presented as frequency histograms, medians, ranges, means, SD and percentages of missing data. Analyses of baseline characteristics, efficacy and safety will be performed in the intent-to-treat population. The ORR and 95% CI of subjects will be estimated on the basis of a binomial distribution. The Kaplan-Meier method will be used to calculate the median PFS and 95% CI. A waterfall plot will be created to illustrate the largest changes by comparing baseline and post-treatment sums of the longest diameters of the

target lesions. All related adverse events will be described in a summary table.

Data management plan and data quality control

The Medidata Rave Electronic Data Capture System was selected for data acquisition and management. A remote network electronic data capture and management model will be used in which physicians enter data directly into the Medidata Rave eCRF without completing paper case report forms, and PDF files will be downloaded for electronic archiving or printed for physical storage. The specific steps of data management are presented in online supplemental figure 1.

The quality control procedures are as follows:

1. Check the original documents. The auditor shall check the data with the original documents, mark them on the eCRF and modify the data inconsistent with the requirements until they are consistent.
2. Monitor inspection. It is required that the total error rate is less than 0.2%, the error rate of key variables is 0% and the error rate of non-key variables is less than 0.5% when monitoring the data verified in original documents.
3. Offline verification by the data administrator. The data administrator will regularly download data, perform data logical verification on key indicators and raise doubts about questionable data.
4. Data review meeting. The issues raised in the database inspection report will be resolved, the data review report will be written and the database will be locked at the same time.

Informed consent

The Cancer Research Patients Committee of Fujian Cancer Hospital has reviewed and approved the informed consent form for this study. It is the responsibility of the investigator to explain in detail to each subject participating in the trial the purpose, methods, benefits and potential dangers of participation and then obtain written informed consent from each subject participating in the study. For subjects who are unable to sign the informed consent, the consent form must be signed by their legal representatives. If any modification/update is made, all subjects shall be informed of new information and given a revised consent form to obtain their consent to continue study participation. A detailed example of an informed consent form is provided in the online supplemental materials.

Ethics and dissemination

The DONATHYCA trial was approved by the Ethics Committee of Fujian Cancer Hospital (K2023-144-02) on 27 July 2023 and registered in the China Clinical Trial Registry on 20 September 2023. The results of the study will be presented at academic conferences and published in scientific publications.

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Acknowledgements We thank Joe Barber Jr, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Contributors JY and HL drafted the protocol, performed the directed statistical analyses and drafted the article. YW directed the writing, review and revision of the article. JY and HL have contributed equally to this work and share first authorship. All authors contributed to the article and approved the submitted version.

Funding This study was supported by the Joint funds for the Innovation of Science and Technology, Fujian Province (No. 2019Y9035), and the Science Fund of Fujian Province Cancer Hospital (2022YNY01).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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