A phase II multicenter trial of the multitargeted kinase inhibitor sulfatinib in advanced medullary thyroid cancer (MTC) and radioiodine (RAI)-refractory differentiated thyroid cancer (DTC)

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Abstract #6037

INTRODUCTION

- Thyroid cancer is the most commonly diagnosed endocrine malignancy. Incidence has increased from 168,000 in 2005 to 334,000 in 2015. About 15% of all cases are in China.[1]
- Sulfatinib is an oral, novel angio-immunokinase inhibitor that selectively inhibits the tyrosine kinase activity associated with vascular endothelial growth factor receptors (VEGFR1, 2 & 3), fibroblast growth factor receptor 1 (FGFR1) and colony stimulating factor-1 receptor (CSF-1R), which are key tyrosine kinase receptors involved in tumor angiogenesis and immune evasion.[2]
- Sulfatinib exhibited an acceptable safety profile and encouraging antitumor activity in patients with advanced solid tumors in a phase I study, particularly neuroendocrine tumors (NETs).[3] In a proof of concept (PoC) phase II study, sulfatinib showed promising efficacy in patients with NETs.[4] Two pivotal registration trials for pancreatic NET patients (SANET-p study, NCT02589821) and non-pancreatic NET patients (SANET-ep study, NCT02588170) are enrolling patients in China.
- This ongoing study is designed to evaluate safety, tolerability and preliminary anti-tumor activity of sulfatinib in patients in China with advanced Medullary Thyroid Cancer (MTC) or radioiodine (RAI)-refractory Differentiated Thyroid Cancer (DTC) (NCT02614495).

OBJECTIVES

PRIMARY OBJECTIVE

- To evaluate the objective response rate (ORR) of sulfatinib in patients with advanced MTC or RAI-refractory DTC.

SECONDARY OBJECTIVES

- To evaluate safety and tolerability of sulfatinib in patients with advanced MTC or RAI-refractory DTC.
- To evaluate disease control rate (DCR), duration of response (DoR), progression-free survival (PFS) and time to response (TTR) of sulfatinib in patients with advanced MTC or RAI-refractory DTC.
- To evaluate pharmacokinetics (PK) of sulfatinib continuous administration in patients with advanced MTC or RAI-refractory DTC.
- To evaluate changes in tumor biomarkers before and after sulfatinib treatment in patients with advanced MTC or RAI-refractory DTC.

EXPLORATORY OBJECTIVES

- To explore the correlation between sulfatinib anti-tumor activity and BRAF, RAS, RET mutation in patients with advanced MTC or RAI-refractory DTC.
- To explore the correlation between sulfatinib anti-tumor activity and biomarkers in the VEGF or FGF signal pathway, include but not limited to VEGF and FGF23.
- To explore the patients with advanced MTC or RAI-refractory DTC change of glucose metabolism before and after sulfatinib treatment through ^{18}F-FDG PET and evaluate it's role in sulfatinib efficacy assessment.

METHOD

PATIENT ELIGIBILITY

Key inclusion criteria

- Patients must have histologically or cytologically documented, locally advanced and/or metastatic MTC or RAI-refractory DTC, which are unresectable or cannot receive external radiotherapy.
- Patients will be eligible if the time between the last dose of ^{131}I therapy and the first dose of the study treatment is more than 6 months.
- RAI-refractory is defined as meeting at least one of the following three criteria:
  - Radiographic evidence of disease progression within the previous 12 months of ^{131}I therapy;
  - At least one lesions that do not demonstrate ^{131}I uptake on any radioiodine scan;
  - Cumulative dose of ^{131}I of > 600 mCi or equivalent dose level, and there is radiographic evidence of disease progression within the previous 12 months before the initiation of study treatment.
- Patients must have radiographic evidence of disease progression within 12 months prior to the first dose of the study treatment.
- Patients must have measurable disease (RECIST 1.1).
- Patients must be ECOG performance status of 0 or 1.

Key exclusion criteria

- Patients have received more than one prior bio-targeted therapy including anti-angiogenesis agent.
- Inadequate organ or bone marrow functions.
- Active infection.
- Current concomitant therapy with any medications that are known to be associated with potent inducers or inhibitors of cytochrome P450 3A4 (CYP3A4).

STUDY DESIGN AND ASSESSMENT

- This is a multicenter, phase II, single-arm, open label clinical trial using Simon's two-stage design. 30-50 patients are expected to be enrolled in 5-10 sites.
  - In stage I, fifteen patients will be enrolled in each cohort (advanced MTC or RAI-refractory DTC).
  - Ten more patients will be enrolled in each cohort in stage II if ≥2 objective responses are observed in the cohort in stage I.
- Patients will receive sulfatinib 300 mg QD continuously (28 days per cycle) until disease progression or intolerable toxicities.
- Adverse Events (AE) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
- The Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 will be used for tumor response evaluation. Tumor response needs to be confirmed at least 4 weeks interval after seeing the initial complete response (CR) or partial response (PR). Tumor assessments will be performed every 8 weeks for the first year, then every 12 weeks thereafter.

RESULTS

PATIENTS

As of 31 March 2017, a total of 20 patients had been enrolled and treated with sulfatinib. Median age is 59.5 (range: 40-78) years, with equal gender distribution.

Table 1. Baseline patients characteristics

Characteristic	N=20
Median Age, years (range)	59.5 (40-78)
Weight, kilograms (range)	65 (41-98)
Sex, n (%)	
Male	10 (50%)
Female	10 (50%)
ECOG PS, n (%)	
0	3 (15%)
1	17 (85%)

Characteristic	N=20
Tumor Type, n (%)	
MTC	7 (35%)
DTC	13 (65%)
Papillary (PTC)	12 (60%)
Follicular (FTC)	1 (5%)
Prior Treatment, n (%)	
Thyroid surgery	20 (100%)
Chemotherapy	2 (10%)
Radiotherapy (except ^{131}I therapy)	0
Bio-targeted therapy*	1 (5%)

*One patient treated by anti-angiogenesis agent (CA4P) before the trial initiation.

EFFICACY

- Sixteen patients had at least one post treatment tumor assessment and therefore constitute Efficacy Evaluable Patients (**EEP**; see Table 2).
  - Among the 16 EEP, four (25%) had confirmed partial response (PR), and the other 12 patients had stable disease (SD) including two unconfirmed PR.
  - The objective response rate (ORR) was 25% in EEP, 30.0% in DTC patients, and 16.7% in MTC patients.
  - The disease control rate (DCR) was 100% in EEP.

Table 2. Best Tumor Response of Evaluable Patients (N=16*)

Response	MTC (N=6) n (%)	DTC (N=10) n (%)	Total (N=16) n (%)
Complete Response (CR)	0	0	0
Partial Response (PR)	1 (16.7)	3 (30.0)	4 (25.0)
Stable Disease (SD)	5 (83.3)	7 (70.0)	12 (75.0)
Progressive Disease (PD)	0	0	0
Not Evaluable (NE)	0	0	0
Objective Response Rate (ORR)	**1 (16.7)**	**3 (30.0)**	**4 (25.0)**
Disease Control Rate (DCR)	**6 (100.0)**	**10 (100.0)**	**16 (100.0)**

*Four patients were not included in the EEP set: three did not complete an assessment; one patient did not have target lesions at baseline.

Figure 1. Best Overall Tumor Response

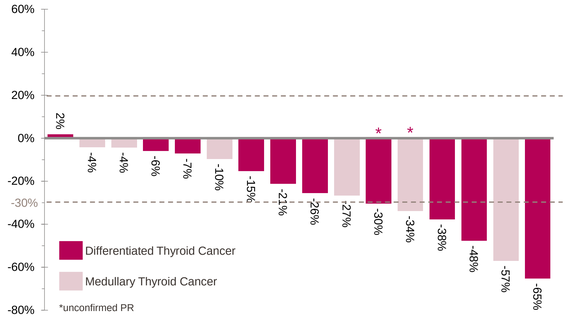
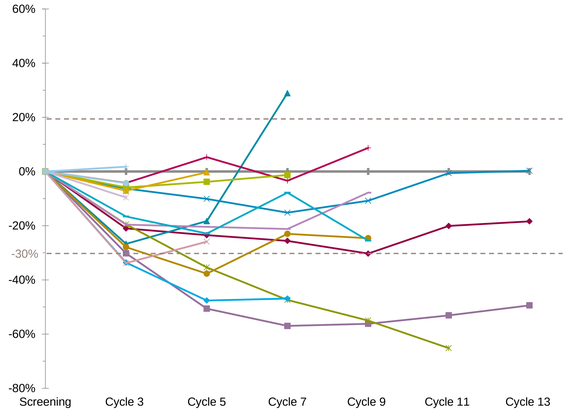


Figure 2. Duration of Response



1 Cycle = 28 days

SAFETY AND TOLERABILITY

- All patients were evaluable for safety as of March 31, 2017. All 20 patients experienced at least one AE. A total of 12 patients (60%) experienced Grade ≥3 AEs. There were five SAEs occurred in four patients, but no fatal outcomes (see Table 3 and Table 6).
- The most frequently (incidence rate ≥ 20%) reported AEs regardless of causality included proteinuria (75%), hypertension (60%), blood bilirubin increased and hypertriglyceridemia (55%, each), diarrhea (45%), haematuria and urinary tract infection (40%, each), blood albumin decrease and hyperuricemia (30%, each), blood creatinine increased and hypocalcaemia (25%, each) (see Table 4).
- The most commonly reported Grade 3 or more severe AEs (incidence rate ≥ 10%) included hypertension (4 patients, 20%), proteinuria (4 patients, 20%) and renal insufficiency (2 patients, 10%) (see Table 5).

Table 3. Overall Adverse Events (All Patients)

All patients (N=20)	n (%)
Any AE	20 (100)
Related AE	20 (100)
Any grade ≥ 3 AE	12 (60)
Related and grade ≥ 3 AE	11 (55)

All patients (N=20)	n (%)
Any SAE	4 (20)
Related SAE	3 (15)
Any Fatal SAE	0

Table 4. Summary of AEs reported by ≥20% patients irrespective of causality

All patients (N=20)	n (%)
Proteinuria	15 (75)
Hypertension	12 (60)
Blood bilirubin increased	11 (55)
Hypertriglyceridemia	11 (55)
Diarrhea	9 (45)
Haematuria	8 (40)

All patients (N=20)	n (%)
Urinary tract infection	8 (40)
Blood albumin decrease	6 (30)
Hyperuricemia	6 (30)
Blood creatinine increased	5 (25)
Hypocalcaemia	5 (25)

Table 5. Summary of Grade ≥3 AEs reported by ≥10% patients irrespective of causality

All patients (N=20)	n (%)
Hypertension	4 (20)
Proteinuria	4 (20)
Renal insufficiency	2 (10)

Table 6. Summary of SAE

Patient No.	SAE Term	CTCAE Grade	Causality	Outcome
S2007	Renal insufficiency	Grade 4	Possibly related	Resolved
S2016	Hepatic function abnormal	Grade 3	Possibly related	Resolved
S2016	Acute renal insufficiency	Grade 4	Possibly related	Resolved
S2020	Intestinal obstruction	Grade 3	Unlikely related	Resolved
S2021	Hyponatremia	Grade 3	Possibly related	Not Resolved

- Nine patients (45%) had dose reduction and 15 (75%) patients had dose interruption during study treatment. Proteinuria was the most common reason leading to dose reduction or interruption.
- A total of seven patients had to discontinue sulfatinib due to disease progression (three patients), unacceptable toxicities (two patients), or patient decision (two patients).

CONCLUSION

The preliminary efficacy of sulfatinib in patients with advanced MTC and RAI-refractory DTC is promising. Sulfatinib is generally tolerated in thyroid cancer patients. Further investigation is warranted.

References

1. C. Fitzmaurice et al. JAMA Oncol 2017 3(4) 524-548; Globocan 2012.
2. J.H. Zhou et al. Abstract #4187. AACR 2017 annual meeting.
3. J.M. Xu et al, Oncotarget 2017 Feb 1 (Epub ahead of print).
4. J.M. Xu, oral presentation, Annual Conference of the ENETS 2017.