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Silvia Martina Ferrari, Marco Centanni, Camilla Virili, Mario Miccoli ...+5 more authors

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# Sunitinib in the treatment of thyroid cancer

Ferrari Silvia Martina[a], Centanni Marco[b], Virili Camilla[b], Miccoli Mario[a], Ferrari Paola[c],

Ruffilli Ilaria[a], Ragusa Francesca[a], Antonelli Alessandro*[a], Fallahi Poupak[a]

[a] Department of Clinical and Experimental Medicine, University of Pisa, Via Savi, 10, I-56126, Pisa, Italy;

[b] Department of Medico-Surgical Sciences and Biotechnologies, "Sapienza" University of Rome, Latina, Italy;

[c] Department of Oncology, University of Pisa, Italy.

***Corresponding author:***

Alessandro Antonelli, Prof
Department of Clinical and Experimental Medicine
University of Pisa
Via Savi, 10, I-56126, Pisa, Italy
Tel: +39-050-992318; Fax: +39-050-553235
e-mail: alessandro.antonelli@med.unipi.it

**Running Title:** Sunitinib in the treatment of TC

**Abstract**

***Background:*** Sunitinib (SU11248) is an oral, small-molecule, multi-targeted tyrosine kinase inhibitor (TKI), that inhibits receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs), c-KIT, fms-related tyrosine kinase 3 (FLT3) and RET. The concurrent inhibition of these pathways reduces tumor vascularization and causes cancer cell apoptosis, inducing a tumor shrinkage. Sunitinib is approved for the treatment of imatinib-resistant gastrointestinal stromal tumor (GIST), renal carcinoma, and pancreatic neuroendocrine tumors.

***Methods:*** We searched the literature on PubMed library.

***Results:*** *In vitro* studies showed that sunitinib targeted the cytosolic MEK/ERK and SAPK/JNK pathways in the RET/PTC1 cell inhibiting cell proliferation and causing stimulation of sodium/iodide symporter (NIS) gene expression in RET/PTC1 cells. Furthermore sunitinib is active *in vitro* and *in vivo* against anaplastic thyroid cancer (ATC) cells. Most of the clinical studies report that sunitinib is effective as first- and second-line TKI therapy in patients with advanced dedifferentiated thyroid cancer (DeTc), or medullary thyroid cancer (MTC). Sunitinib 37.5 mg/day is well tolerated, and effective. The most common adverse events include decreases in blood cell counts (especially leukocytes), diarrhea, fatigue, hand-foot skin reaction, nausea, musculoskeletal pain, and hypertension.

***Conclusion:*** Even if sunitinib is promising in the therapy of differentiated thyroid carcinoma (DTC), until now no phase III studies have been published, and additional prospective researches are necessary in order to evaluate the real efficacy of sunitinib in aggressive thyroid cancer.

**Keywords:** sunitinib, thyroid, tyrosine kinase, anaplastic thyroid cancer, medullary thyroid cancer, papillary thyroid cancer, follicular thyroid cancer

## 1. Introduction

The incidence of differentiated thyroid cancer (DTC) has been increasing in the last 40 years [1]; it is the 7$^{th}$ most common cause of new malignancy in the US (2007) for women, and the 14$^{th}$ in men (8070 cases in men) [2].

Among risk factors for DTC, there are: ionizing radiations exposure during childhood or adolescence, that can lead to papillary thyroid cancer (PTC) [3], and exposure to secondary radiations, or nuclear explosions or nuclear accidents [4, 5]; even low doses of radiations can lead to the onset of thyroid nodules and cancer [6, 7].

Considering the other risk factors, iodine deficiency is associated with a higher frequency of follicular thyroid cancer (FTC), while an increased frequency of PTC has been demonstrated in iodine deficient areas, after the introduction of iodine prophylaxis [8, 9]. PTC is also associated with Hashimoto's thyroiditis, as thyroid lymphoma [10-13].

Total thyroidectomy is the election treatment for aggressive PTCs and FTCs [5], while radioiodine remnant ablation with $^{131}$I is indicated only in aggressive PTCs and FTCs [14]. After surgery, patients with PTC and FTC are followed by basal and rTSH-stimulated thyroglobulin (Tg) determination, and by neck ultrasonography [5, 15, 16].

About 5% of cases develop tumor dedifferentiation that is characterized by a more aggressive behaviour and loss of iodide uptake ability. Radiotherapy and conventional chemotherapy are slightly important in the treatment of dedifferentiated papillary thyroid cancer (DePTC) [17]. For this reason, the management of DePTC patients requires new therapeutic options.

In the last decades, interesting progresses in the understanding of the molecular pathogenesis of TC have been made. Genetic and epigenetic alterations have a key role in these pathways, as gene copy-number gain, mutations, and aberrant gene methylation. Most of these molecular alterations can be considered new diagnostic and prognostic molecular markers and therapeutic targets for TC, and tyrosine kinase inhibitors (TKIs), that can modulate TK-dependent oncogenic pathways, can be considered as an option of systemic treatment in case of progressive, aggressive refractory cancers.

The aim of the present review article, conducted searching the concerning literature on PubMed library, was to evaluate the role of sunitinib in the treatment of thyroid cancer (TC), and its real efficacy.

### 1.1. Molecular pathways involved in the development of TC

In PTCs, BRAF mutations are found in approximately 40-50%, rearranged during transfection/PTC (RET/PTC) in 30-40%, and RAS mutations in about 10%, with no overlap among these mutations. In DePTCs [18, 19], an increased prevalence of BRAF mutations (up to 70%) has been shown.

In FTCs, PAX8/peroxisome proliferator-activated receptor (PPAR)γ rearrangement (PAX8/PPARγ) occurs in about 35%, and RAS mutations are found in 40-50% of tumors [20, 21].

Mutations of the RET proto-oncogene play a casual role in the familial forms and also in the sporadic forms of medullary thyroid carcinoma (MTC).

The knowledge of the molecular pathways involved in the oncogenesis of TC has permitted the development of new drugs able to block oncogenic kinases (V600EBRAF, RET/PTC) or signaling kinases [as vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptors (PDGF-Rs)] in cellular growth and proliferation [19].

### 1.2. TKIs

TKIs are compounds with low molecular weights able to modulate TK-dependent oncogenic pathways, competing with the ATP-binding site of their catalytic domain [22]. The occupation of the ATP-binding site reduces autophosphorylation and TK activation, inhibiting the following activation of intracellular signaling pathways. Rearranged during transfection (RET)/PTC gene rearrangements, RET mutations, BRAF mutations, RAS mutations, and VEGFR-2 angiogenesis pathways are some of the known pathways determinant in the development of TC. TKIs can be specific to one or several TKs; in fact, a single TKI may target multiple TKs [23].

TKIs are currently used as therapies of aggressive TC, including DTC, MTC and anaplastic thyroid cancer (ATC), thanks to their capability of inducing clinical responses and stabilization of disease. Vandetanib and cabozantinib have been approved for the treatment of MTC, whereas sorafenib and lenvatinib for DTC refractory to radioactive iodine (RAI) [24-27]. These drugs prolong median progression-free survival (PFS); however

major side effects are common. New efforts are made to find new more effective and safe compounds, and to personalize the therapy in each TC patient.

### 1.2.1. Sunitinib

Sunitinib (sutent®, Pfizer; SU11248) is an oral, multi-targeted TKI with a low molecular weight [28]. Sunitinib inhibits PDGF-Rs and VEGFRs. The simultaneous inhibition of these receptors reduces tumor vascularization and triggers cancer cell apoptosis, inducing a tumor shrinkage [29, 30]. Sunitinib also inhibits c-KIT, the receptor TK that (when mutated and activated) drives gastrointestinal stromal tumors (GIST) cell [31]. In addition, sunitinib inhibits other TKIs receptors: fms-related tyrosine kinase 3 (FLT3), RET, CD114, CD135 [31].

Imatinib was the first cancer agent efficacious in metastatic GIST, even if about 20% of patients are not responsive to imatinib (primary resistance), and a secondary resistance can be developed in 50% of the cases by 2 years [32]. In a phase III clinical trial, the patients who were not treated with imatinib owing to primary or secondary resistance, or intolerance, were administered with sunitinib or placebo. Median time to tumor progression was more than 4-fold higher considering sunitinib (27 weeks) with respect to placebo (6 weeks), and the relative risk of disease progression or death was decreased by 67% by sunitinib [32]. For these reasons, it was approved by the Food and Drug Administration (FDA) for the treatment of imatinib-resistant GIST on January 26, 2006.

Sunitinib is approved as therapy of metastatic renal cell carcinoma (RCC), that is usually resistant to chemotherapy or radiation. In a phase III study, median PFS was significantly longer in patients treated with sunitinib (11 months) than in the ones administered with interferon (IFN)α (5 months), (hazard ratio 0.42) [33, 34], as quality of life. In the secondary endpoints, 28% had significant tumor shrinkage with sunitinib with respect to 5% with IFNα. At the end of the study the primary endpoint of median PFS was still better with sunitinib (11 months versus 5 months for IFNα, $P<0.000001$), as objective response rate (ORR) (39-47% for sunitinib versus 8-12% with IFNα) [35].

Moreover, in November 2010, sutent was approved by EMA for the therapy of 'unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumors with disease progression in adults', and FDA approved it in

'progressive neuroendocrine cancerous tumors located in the pancreas that cannot be removed by surgery or metastatic' in May 2011 [36, 37].

The effectiveness of sunitinib has been also assessed in other solid tumors, like metastatic breast, lung, and colorectal cancers [38].

### 1.4. Sunitinib in TC

#### 1.4.1. *In vitro* studies

In a first *in vitro* study, SU11248 was shown to inhibit phosphorylation of the synthetic TK substrate peptide E4Y by RET/PTC3 dose-dependently. SU11248 caused a complete morphological reversion of transformed NIH-RET/PTC3 cells and inhibited the growth of TPC-1 cells with an endogenous RET/PTC1 [39]. This study suggested sunitinib could be effective in DTC. In a further study the effects of sunitinib on cell growth, signal transduction pathways, and thyroid-specific gene expression in PTC cell lines that had the RET/PTC1 rearrangement were evaluated. Sunitinib targeted the cytosolic MEK/ERK and SAPK/JNK pathways in the RET/PTC1 cell lines, suggesting that blocking these pathways is at least in part as blocking the mechanism by which sunitinib inhibits cell proliferation and causes stimulation of sodium/iodide symporter (NIS) gene expression in RET/PTC1 cells [40]. The effect of sunitinib on PTC cells harboring RET/PTC rearrangement and BRAF mutation was evaluated, too, using TPC-1M, SNU-790, and B-cPAP cell lines. Cell growth of PTC cells with RET/PTC rearrangement was significantly inhibited at low doses of sunitinib, whereas that of BRAF mutated cells required higher doses. This study suggested that sunitinib significantly inhibits RET/PTC rearrangement cells but not BRAF mutated cells [41]. Another study evaluated sunitinib effectiveness in human cell lines obtained from ATCs (8505C, CAL-62, and C643). Sunitinib had little or no effect on the growth or differentiation of ATC cells, thus suggesting that it is unlikely to be effective in the treatment of ATC [42]. The effect of activating somatic mutations in the KRAS and BRAF genes on the responsiveness to sunitinib was evaluated in a panel of TC cell lines harboring wild-type KRAS and BRAF genes, the RET/PTC1 rearrangement, the G12R KRAS, or the V600E BRAF mutation. Results suggested that the constitutive activation of the RAS/RAF/ERK pathway may favor resistance to sunitinib in TC cells [43]. In another recent study, proliferation and apoptotic assays were done on human dermal microvascular endothelial and on BRAF-

or H-ras-mutated ATC cells (8305C and FB3, respectively) after *in vitro* exposure to sunitinib for 72 hours. The antiproliferative and proapoptotic effect of sunitinib was reported in endothelial and ATC cells. Sunitinib administration *in vivo* significantly inhibited tumor growth, suggesting that it is active *in vitro* and *in vivo* against activated endothelial and ATC cells inhibiting the phosphorylation of Akt and ERK1/2 and through the down-regulation of cyclin-D1 [44].

### 1.4.2. *In vivo* anecdotal studies.

A first clinical study in two patients with progressive metastatic DTC demonstrated sustained clinical responses to sunitinib over a duration of 4 years [45].

In a 55-year-old man with locally advanced MTC, without germinal and/or somatic RET mutations, it was administered sunitinib (50 mg/day for 28 days, followed by 14 days of no treatment; four consecutive cycles), and an early and dramatic tumor reduction of a cervical lymph node conglomerate was observed [46]. In another study conducted in 2 patients, sunitinib appeared to be effective in patients with widely metastatic, progressive DTC [47]. The administration of sunitinib resulted in partial disease response in other patients with progressive metastatic PTC or MTC [48-53]. Another study described the case of a patient with ATC and a significant gross residual disease treated with intensity-modulated radiotherapy with concurrent chemotherapy and sunitinib who had a complete response and remains without evidence of disease more than 18 months after the diagnosis [54]. Also another case report showed clinical and visual activity in an ATC patient, treated with sunitinib as a salvage treatment, who had not previously received systemic chemotherapy treatment [55].

### 1.4.3. Clinical studies

In a first phase II study sunitinib was administered (50 mg/day) to 37 DTC patients, and 6 MTC patients, with aggressive disease. In DTC patients, 13% achieved partial response (PR), 68% a stable disease (SD), and 10% had a progressive disease (PD). In MTC patients, 0% achieved PR, 83% a SD, and 17% had a PD [56]. In a second trial [57], 18 patients with metastatic, RAI-refractory and evidence of flurodeoxyglucose positron emission tomography (FDG-PET) avid TC (3 MTC, 15 DTC) were enrolled. Sunitinib was administered at 37.5 mg daily and FDG-PET was done in 16 patients at the beginning and after 7 days of therapy. The FDG-PET response rate was reported in 7 patients, all with DTC histology; the Response Evaluation Criteria in Solid

Tumors (RECIST) response rate was evaluated at the time of report. One patient died for gastrointestinal bleeding [57] . The phase II Trial of sunitinib in Patients with Locally Advanced or Metastatic ATC or DTC (THYSU) was designed to assess the effectiveness of sunitinib for progressive, locally advanced, or metastatic TC. According to histology, 2 cohorts of patients were examined: DTC and ATC on one hand, and MTC on the other. Patients were administered with sunitinib at the standard dose of 50 mg/day, 4 weeks every 6 weeks. The mean follow-up duration was 6.2 months (range, 1.2–10.3 months). Two patients had a confirmed PR, 3 an unconfirmed PR (33.3%), and 4 had SD for ≥12 weeks (26.7%), with an overall mean tumor shrinkage rate of 27.3% [58, 59]. The effectiveness of sunitinib (at 37.5 mg/die on a continuous basis) in patients with FDG-PET-avid, iodine-refractory well-DTC (WDTC) and MTC was evaluated in a phase II study [60]. Thirty-five patients were enrolled (7 MTC, 28 WDTC), and 33 patients were evaluable for disease response. The primary end point, ORR per RECIST, was 11 patients (31%), there were 1 complete response (3%), 10 PR (28%), and 16 patients (46%) with SD [60]. De Souza et al. carried on an open-label multicenter phase II trial in order to assess the effectiveness of sunitinib in patients with MTC and whether RET mutations can predict response. Twenty-five patients with MTC, showing disease progression by the first 6 months and not willing to undergo surgery or radiotherapy, were administered with sunitinib 50 mg at a 4/2 week schedule. Responses were monitored by RECIST and serum calcitonin measured every 12 weeks. Median follow-up was 11 months (range, 1-34); median age was 51 years (23-74); 12 patients (50%) were male; RET activating mutations were reported in 11 (8 somatic and 3 germline; 85%) among 13 evaluated tumors. PR was achieved in 8 (35%) patients with a median duration of response of 37 weeks (22-106+). Thirteen (57%) had SD with a median duration of 32 weeks (12-147+). These results suggested that sunitinib has activity in MTC, with an overall response rate of 35% and clinical benefit rate (PR + SD) of 91% (in patients with/without RET mutations; in particular the M918T RET mutation could be linked to a lasting response [61]). Discordant results were reported in 12 sunitinib treated patients with DTC who had a PR only in 8% [62]. In a single center, not randomized, open-label, phase II clinical trial, 23 patients with advanced DTC were enrolled and were treated with a starting daily, oral dose of 37.5 mg sunitinib. Six (26%) patients achieved a PR, and 13 (57%) had SD for a clinical benefit rate (PR+SD) of 83%. The overall median PFS was 241 days (interquartile limits, 114-518). The Authors suggested that sunitinib exhibits significant anti-tumor activity in patients with advanced DTC [63]. Diez et al. evaluated sunitinib in 11 consecutive patients (6 men, 5 women, mean age 63.0 ± 12.9 years) with advanced PTC (7 patients) or FTC (4 patients) not suitable for curative surgery or RAI therapy. One patient (9 %) had a complete response, 2 patients (18 %) a PR and 5 patients (45 %) a SD; ORR was 27 % and disease control rate 72 % [52]. A very recent

multicentric retrospective analysis was performed to evaluate the effectiveness of sunitinib in patients with progressive RAI refractory (RAIR) TC in 57 patients (50.8%, men) mean age 62.2 years (range 43-80 years). Sunitinib was the first-line TKI treatment for 32 (56.1%) patients and the second-line TKI treatment for 25 (43.9%) patients. As first-line TKI therapy, it showed ORR 46.9% (15/32 patients), disease control rate ≥6 months 75% (24/32 patients), median OS and PFS 30.0 (range 19.0-53.0) and 15 (range 7.0-21.0) months, respectively. As second-line TKI therapy, it showed ORR 20% (5/25 patients), disease control rate ≥6 months 60% (15/25 patients), median OS and PFS 13 (range 8.0-20.0) and 6 (range 5.0-11.0) months, respectively [64].

A phase II trial, that is still ongoing, but not recruiting participants, evaluates the effectiveness of sunitinib malate in patients with TC (DTC and MTC) that did not respond to RAI and cannot be removed by surgery. Sunitinib malate can stop the growth of tumor cells by blocking some of the enzymes needed for cell growth and by blocking blood flow to the tumor [65].

The above mentioned studies suggest the efficacy of sunitinib as first- and second-line TKI therapy in patients with advanced DTC. However, additional prospective studies are necessary to assess the efficacy of sunitinib in RAIR TC.

### 1.4.4. Tolerability

The most common AEs included grades 1 and 2 decreases in blood cell counts (especially leukocytes), diarrhea, fatigue, hand-foot skin reaction, nausea, musculoskeletal pain, and hypertension [52, 60, 63]. Patients (30 subjects were evaluable) with advanced solid organ malignancies were administered with bortezomib weekly with sunitinib once-daily for 4 weeks, every 6 weeks, in a phase I trial with a Bayesian continual reassessment method, assessing bortezomib and sunitinib to evaluate the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), and recommended doses of their combination. At the beginning the doses of sunitinib and bortezomib were 25 mg and 1 mg $m^{-2}$, respectively. As sunitinib was increased, DLTs of grade 4 thrombocytopenia (14%) and neutropenia (6%) were reported with sunitinib 50 mg and bortezomib 1.3 mg $m^{-2}$. The following experience reported tolerability and activity for sunitinib 37.5 mg and bortezomib 1.9 mg $m^{-2}$. Common grade 3/4 toxicities were neutropenia, thrombocytopenia, hypertension, and diarrhea. The recommended doses for additional studies are bortezomib 1.9 mg $m^{-2}$ and sunitinib 37.5 mg. Four PR and SD >6

months in an additional 6 patients were reported, suggesting bortezomib and sunitinib are well tolerated and exert anticancer effect, especially in TC [66].

### 1.5. Limits and drug resistance

Despite TKIs have a minor toxicity respect to cytotoxic chemotherapy, they can lead to significant side effects, like diarrhea, fatigue, hypertension, vomiting, mucositis, hand-and-foot syndrome, cutaneous rash, nausea, and thyroid dysfunction, too [67], causing the suspension of the treatment with TKIs.

Patients with DTC following a TKIs therapy in the clinical trials had contrasting outcomes, probably caused by drug resistance arising from the activation of alternate mitogenic signals [68].

TKIs act as an antiangiogenetic drugs, blocking tumor growth without removing tumor cells.

For this reason, the combination of TKIs has been recently proposed [68], even if possible interactions between them are still unknown [69].

Testing the sensitivity of primary TC cells from each subject to different TKIs could ameliorate the efficacy of the treatments [70, 71].

Disease orientated *in vitro* drug screening in human tumor cells has some predictive value for the effect of clinical responses [72, 73], and could prevent the administration of ineffective chemotherapeutics to patients [74].

Chemosensitivity tests *in vitro* gave a prediction of *in vivo* efficacy in 60% of cases [75], while there is an association of about 90% between a negative chemosensitivity test *in vitro* and an ineffectiveness of the chemotherapy *in vivo* [73]; this could permit to avoid the administration of ineffective drugs to patients. While until now primary TC cell cultures have been established from surgical biopsies, obtained from therapeutic or diagnostic procedures, we have recently reported the possibility to obtain primary cultures form fine-needle aspiration (FNA) cytology samples of ATC (FNA-ANA); this paves the way to the use of FNA-ANA to assess the sensitivity to different drugs in each patient, avoiding unnecessary surgical procedures and the administration of ineffective drugs [70, 75-85].

**Conclusion**

Sunitinib (SU11248) is an oral, multi-targeted TKI with a low molecular weight, that inhibits receptors for PDGF-Rs and VEGFRs, c-KIT [the receptor TK that (when mutated and activated) drives GIST cell], FLT3, RET, CD114, CD135. The concurrent inhibition of the above mentioned pathways reduces tumor vascularization and causes cancer cell apoptosis, inducing a tumor shrinkage. Sunitinib is approved for the treatment of imatinib-resistant GIST, renal carcinoma, and pancreatic neuroendocrine tumors. *In vitro* studies showed that sunitinib targeted the cytosolic MEK/ERK and SAPK/JNK pathways in the RET/PTC1 cell lines, suggesting that blocking these pathways is at least in part as blocking the mechanism by which sunitinib inhibits cell proliferation and causes stimulation of NIS gene expression in RET/PTC1 cells [40]. Furthermore sunitinib is active *in vitro* and *in vivo* against activated endothelial and ATC cells inhibiting the phosphorylation of Akt and ERK1/2 and through the down-regulation of cyclin-D1 [44]. Many **anecdotal** studies have suggested the efficay of sunitinib in patients with dedifferentiated thyroid cancer (DeTc), MTC or even ATC. Most of clinical studies report an efficacy of sunitinib, as first- and second-line TKI therapy in patients with advanced DeTc, or MTC. Sunitinib 37.5 mg/day is well tolerated, and effective.

The phase II Trial of sunitinib in Patients with Locally Advanced or Metastatic ATC or DTC (THYSU) has shown the effectiveness of sunitinib for progressive, locally advanced, or metastatic TC.

An open-label multicenter phase II trial has assessed the effectiveness of sunitinib in 25 patients with MTC (50 mg at a 4/2 week schedule) and whether RET mutations can predict response [RET activating mutations were reported in 11 (8 somatic and 3 germline; 85%)]. The results suggested that sunitinib has activity in MTC, with an overall response rate of 35% and clinical benefit rate (PR + SD) of 91% (in patients with/without RET mutations).

The most common AEs include decreases in blood cell counts (especially leukocytes), diarrhea, fatigue, hand-foot skin reaction, nausea, musculoskeletal pain, and hypertension. Even if sunitinib is promising in the therapy of DTC, until now no phase III studies have been published, and supplementary prospective researches are required to assess the real effects of sunitinib in aggressive thyroid cancer.

## Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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Table **1**: Clinical trials of sunitinib in patients with thyroid cancer.

| **Drug** | **Thyroid cancer** | **Responses** | | | | | **Authors** |
|---|---|---|---|---|---|---|---|
| | | **PR**<br><br>**N° pts (%)** | **SD**<br><br>**N° pts (%)** | **PD**<br><br>**N° pts (%)** | **ORR** | **PFS (months)** | |
| Sunitinib | 37 DeTC<br><br>6 MTC | 5 (13%) DeTC | 25 (68%) DeTC<br><br>5 (83%) MTC | 4 (10%) DeTC<br><br>6 (17%) MTC | Not reported | Not reported | Cohen et al. [56] |
| Sunitinib | 7 MTC<br><br>28 DeTC<br><br>(33 were evaluable) | 10 (30%) | 16 (48%) | 6 (18%) | 11 (33%) | 12.8 | Carr et al. [60] |
| Sunitinib | 41 DeTC<br><br>4 ATC<br><br>26 MTC | 8 DeTC + ATC (18%)<br><br>10 MTC (38%) | 23 DeTC + ATC (51%)<br><br>13 MTC (50%) | 7 DeTC + ATC (16%)<br><br>1 MTC (4%) | 9 DeTC + ATC (20%) | 13.1 DeTC<br><br>16.5 MTC | Ravaud et al. [58] |
| Sunitinib | 23 MTC<br><br>(evaluable) | 8 (34.8%) | 13 (56.5%) | 2 (8.7%) | 35% | | De Souza et al. [61] |
| Sunitinib | 12 DTC | 1 (8%) | 11 (92%) | 0 | 8% | 6.5 | Massicotte et al. [62] |
| Sunitinib | 23 DTC | 6 (26%) | 13 (57%) | 9 (39%) | 6 (26%) | 8 | Bikas et al. [63] |
| Sunitinib | 11 DeTC | 2 (18%) | 5 (45%) | 3 (27%) | 3 (27%) | | Dìez et al. [52] |
| Sunitinib | 32 DeTC<br><br>(first-line TKI)<br><br>25 DeTC<br><br>(second-line TKI) | Not reported | Disease Control Rate<br><br>24 (75%)<br><br>(Disease control rate ≥ six month was defined as the proportion of patients with CR, PR and stable disease (SD) ≥ six month) | 6 (10.5%) | 35.1% (for all patients) | 10.2 months (range 6-13 for all patients) | Atallah et al. [64] |

Anaplastic thyroid cancer (ATC); **differentiated thyroid cancer (DTC)**; dedifferentiated thyroid cancer (DeTC); medullary thyroid cancer (MTC); **overall response rate (ORR), (defined as "complete response plus partial response")**; progressive disease (PD); progression-free survival (PFS); partial response (PR); stable disease (SD).