Sorafenib in metastatic thyroid cancer

*Jaume Capdevila, Lara Iglesias¹, Irene Halperin², Ángel Segura³,
Javier Martínez-Trufero⁴, Maria Ángeles Vaz⁵, Jesús Corral⁶,
Gabriel Obiols⁷, Enrique Grande⁵, Juan Jose Grau⁸ and Josep Tabernero*

Medical Oncology Department, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, P. Vall d'Hebron 119-129, 08035 Barcelona, Spain

¹Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain

²Endocrinology Department, Hospital Clinic, Barcelona University, Barcelona, Spain

³Medical Oncology Department, La Fe University Hospital, Valencia, Spain

⁴Medical Oncology Department, Hospital Miguel Servet, Zaragoza, Spain

⁵Hospital Universitario Ramón y Cajal, Madrid, Spain

⁶Medical Oncology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain

⁷Endocrinology Department, Vall d'Hebron University Hospital, Barcelona University, Barcelona, Spain

⁸Medical Oncology Department, Hospital Clinic, Barcelona, Spain

(Correspondence should be addressed to J Capdevila; Email: jacapdevila@vhebron.net)

Abstract

Although thyroid cancer usually has an excellent prognosis, few therapeutic options are available in the refractory setting. Based on the recent results of phase II studies with tyrosine kinase inhibitors, we designed a retrospective analysis of patients with metastatic thyroid cancer treated with sorafenib in seven Spanish referral centers. Consecutive patients with progressive metastatic thyroid cancer (papillary, follicular, medullary, and anaplastic) not suitable for curative surgery, radioactive-iodine therapy, or radiotherapy were treated with sorafenib 400 mg twice a day. The primary end point was objective response rate (RR). Secondary end points included toxicity, median progression-free survival (mPFS), median overall survival (mOS), and correlation between tumor marker levels (thyroglobulin, calcitonin, and carcinoembryonic antigen) and efficacy. Between June 2006 and January 2010, 34 patients were included in the study. Sixteen patients presented differentiated thyroid carcinomas (DTC) of which seven (21%) were papillary, nine (26%) follicular, 15 (44%) medullary (MTC), and three (9%) were anaplastic (ATC). Eleven (32%) patients achieved partial response and 14 (41%) had stable disease beyond 6 months. Regarding histological subtype, RRs were 47% (seven of 15) for MTC, 19% (three of 16) for DTC, and 33% (one of three) for ATC. With a median follow-up of 11.5 months, mPFS were 13.5, 10.5, and 4.4 months for DTC, MTC, and ATC respectively. Tumor markers were evaluated in 22 patients, and a statistically significant association was observed between RR and decrease in tumor marker levels $>50\%$ ($P=0.033$). In this retrospective trial, sorafenib showed antitumor efficacy in all histological subtypes of thyroid cancer, warranting further development in this setting.

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Introduction

Several translational and clinical studies have been designed based on the knowledge of the main molecular steps that lead to the transformation of the normal follicular cell into an invasive thyroid carcinoma, whose results are leading to a more optimistic outcome for the treatment of these patients. Thyroid cancer has become one of the most fascinating models of carcinogenesis and is a particularly promising paradigm for targeted therapy.

A multistep model has been proposed as a mechanism for the neoplastic process in thyroid cancer, involving the main genetic mutations that provoke the tumor-initiating process in a follicular cell, and the phenomenon of oncogenic addiction to these particular mutations that makes them particularly interesting for directed therapy (Puxeddu *et al.* 2011). One of the most important activating genetic mutations involves the RET/PTC–RAS–RAF–MAPK axis. For hereditary medullary thyroid cancer (MTC), mutations

in the *RET* gene are essential in more than 95% of cases and are also important for the development of sporadic MTC (50% of cases) (Nikiforova & Nikiforov 2008). Activating mutations in protein kinase B-type RAF (BRAF) kinase play a key role in the carcinogenesis of papillary thyroid cancer (PTC) in up to 45% of cases, as do *RAS* mutations (10%), as well as rearrangements in the *RET* gene (*RET*/PTC) in 5–30% of cases. These mutations have also been described in follicular thyroid carcinomas (FTC) affecting, in more than 40% of cases, three genes in the *RAS* proto-oncogene family (*HRAS*, *NRAS*, and *KRAS*). Genomic rearrangements occur in up to 50% of FTCs involving a translocation event between chromosome regions 3p25 and 2q13, which results in a fusion protein (paired box gene 8 (*PAX8*) with the peroxisome proliferator-activated receptor γ (*PPAR* γ (*PPARG*)) gene). Genetic alterations in the *RAS*–*BRAF* pathway have also been identified in poorly differentiated and anaplastic PTCs with the accumulation of other important protein mutations such as p53 (TP53), β -catenin, or phosphatidylinositol-3-kinase (PI3K (PIK3CA)). Additionally, upregulation of vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR (PDGFRB)) expression has been well described in thyroid cancer and correlated with tumor stage, size, and lymphatic and distant tumor spread with a detrimental impact on survival (Yu et al. 2005).

Sorafenib (BAY 43-9006) is the first compound capable of inhibiting all RAF kinases that are administered in clinical practice. Moreover, sorafenib targets a panel of tyrosine kinase receptors such as VEGF receptors 1–3, PDGFRB, and RET, which give sorafenib not only proapoptotic properties but also antiangiogenic effects that are of special interest in thyroid carcinomas (Wilhelm et al. 2004).

We report the results of a retrospective population-based study evaluating the activity of sorafenib in patients with metastatic thyroid cancer.

Materials and methods

Patients

Eligible patients were ≥ 18 years old with histologically confirmed thyroid carcinoma (papillary, follicular, medullary, or anaplastic subtypes) for which no curative or standard palliative therapies were available. Patients had evidence of disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) in the 12 months before entering the study, and all patients had measurable disease according to RECIST criteria. Previous therapies

such as radioiodine therapy, radiotherapy, chemotherapy, or biologic treatment were permitted. Other inclusion criteria included Eastern Cooperative Oncology Group performance status (ECOG) ≤ 2 with preserved renal, hepatic, and bone marrow function. All patients provided written informed consent and were included in the Spanish compassionate use program. Also, authorizations from the hospitals' pharmacy departments, management, and central government for the off-label use sorafenib in patients with metastatic thyroid carcinoma were obtained for each patient.

Study design

This was a retrospective longitudinal study of a group of patients included in the Spanish off-label program of sorafenib for the treatment of metastatic thyroid carcinoma. Patients included in the analysis had received sorafenib 400 mg twice a day as long as it provided clinical benefit or until unacceptable toxicity occurred. Patients with papillary, follicular, medullary, and anaplastic subtypes were included. The study was performed in accordance with local legislation in seven Spanish referral centers. Clinical benefit was defined as partial response (PR) or stable disease (SD). Patients were withdrawn from the study after radiologically confirmed tumor disease progression according to RECIST. Patients were evaluated clinically every month and radiologically every 2–3 weeks. A cycle was defined as 4 weeks, and tumor evaluation was performed by computed tomography (CT) scan or magnetic resonance imaging (MRI) every 8–12 weeks. Tumor marker evaluation, carcinoembryonic antigen (CEA), thyroglobulin, and calcitonin tests were performed every 8–12 weeks. Dose adjustments were made according to toxicity profile.

Study end points and statistical analysis

The primary end point was efficacy evaluated in terms of response rate (RR) according to RECIST v1.0 (Therasse et al. 2000). Secondary end points included toxicity profile, evaluated by means of the Common Terminology Criteria for Adverse Events v3.0. (CTCAE v3.0), median progression-free survival (mPFS), median overall survival (mOS), and the correlation between efficacy and tumor marker levels: thyroglobulin for differentiated thyroid cancer (DTC) that included PTC and FTC, and calcitonin and CEA for MTC.

Statistical analyses of survival were performed using a log-rank of Kaplan–Meier survival estimates and χ^2 distribution for the correlation between tumor markers and efficacy.

Results

Between June 2006 and January 2010, 34 consecutive patients included in the Spanish off-label program of sorafenib for the treatment of metastatic thyroid carcinoma were included in the study, whose baseline characteristics are summarized in Table 1. Of the 34 patients with confirmed thyroid cancer, seven (21%) were papillary, nine (26%) follicular, 15 (44%) medullary, and three (9%) were anaplastic. At baseline, 33 patients (97%) had previously undergone surgery, 19 (56%) had received radiotherapy, 13 (38%) radioactive iodine therapy, 11 (32%) chemotherapy, seven (20%) had received somatostatin analogs, and one patient (3%) had received previous treatment with a tyrosine kinase inhibitor (TKI), namely sunitinib. All patients presented disease progression according to RECIST criteria before inclusion in the trial.

Efficacy

A total of 32 patients were evaluable for radiological response, but all 34 patients were included in the intention-to-treat analysis. Eleven patients reached PR and 14 reached SD beyond 6 months. The disease control rate (PR+SD) was 73%. The PR rate by histological subtype was 7/15 (47%) for patients with MTC, 3/16 (19%) for patients with DTC, and 1/3 (33%) for patients with anaplastic carcinomas. Disease control rate for patients with MTC was 87%, and for patients with DTC, it was 69% (Table 2).

With a median follow-up of 11.5 months, mPFS was 10.5 months (95% CI: 6.13–14.87) for the whole group of patients including all subtypes. As expected, mPFS differed according to thyroid carcinoma subtype (Fig. 1), from 4.4 months (95% CI: 2.30–6.57) in the

Table 1 Patient characteristics

Total no. of patients	34
Gender M/F (no.)	16/18
Median age (range)	57.3 years (range 28.8–84.6)
ECOG/PS	n (%)
0	5 (15)
1	20 (59)
2	9 (26)
Tumor subtypes	n (%)
Papillary	7 (23)
Follicular	9 (26)
Medullary	15 (44)
Anaplastic	3 (7)
Previous therapies	n (%)
Surgery	33 (97)
Radiotherapy	19 (56)
Radioiodine therapy	13 (38)
Chemotherapy	11 (32)
Somatostatin analogs	7 (20)

Table 2 Tumor response by histology subtypes

	PR	SD	PD
Papillary	14% (1/7)	43% (3/7)	43% (3/7)
Follicular	22% (2/9)	55% (5/9)	11% (1/9)
DTC	19% (3/16)	50% (8/16)	25% (4/16)
Medullary	47% (7/15)	40% (6/15)	7% (1/15)
Anaplastic	33% (1/3)	0%	66% (2/3)

anaplastic population to 13.3 months (95% CI: 6.28–20.45) in patients with DTC and 10.5 months (95% CI: 4.49–16.51) in those with MTC. In terms of OS, the median for the whole group of patients was 23.6 months; when considering the different subtypes, the values were 5 months for the anaplastic tumor population and 23.6 months for the DTC population, although this value was not reached in patients with MTC (Fig. 2).

Marker correlation

Correlation between tumor marker decrease >50% and tumor response to sorafenib was analyzed. Thyroglobulin was used for DTC and calcitonin and/or CEA for MTC. Twenty-eight (82%) patients were evaluated for tumor marker response. In 16 patients, there was a decrease in any tumor marker >50% from baseline value, eight of whom achieved PR. Of the 12 patients who did not show a decrease in tumor markers, only one patient presented a PR. A statistically significant association was observed between >50% decrease of any tumor marker and the probability of achieving a tumor response according to RECIST criteria ($P<0.05$, χ^2 analysis). Analysis by tumor subtype and tumor marker type did not show statistical significance owing to the low number of patients in each group.

Toxicity

The most common side effects (frequency $\geq 5\%$) were hand-foot syndrome, diarrhea, rash, asthenia, anorexia, stomatitis, hypertension, and abdominal pain. The majority of side effects were controlled with treatment delays or dose reductions. Table 3 summarizes all the toxicity profile observed during the study period. The toxicity profile was similar to that observed in patients with other primary tumors. Twelve (35%) patients required a dose reduction due to toxicity. No patient required increased levothyroxine dose while on treatment with sorafenib. There was one death due to intracranial hemorrhage during the study, and a relationship with sorafenib cannot be ruled out.

Figure 1 Median progression-free survival curves. Statistically significant differences were observed between DTC and anaplastic and also between medullary and anaplastic. No differences were observed for DTC and MTC.

Discussion

Until recently, medical management of advanced thyroid cancer refractory to standard treatments has been particularly challenging. Classical DNA-damaging drugs have demonstrated limited activity in this setting with no impact on survival. The knowledge of key mutational events in some genes including *BRAF* and *RET* that affect early stages of thyroid carcinogenesis has opened up a new scenario for targeted therapies. Sorafenib is the only available drug that targets BRAF, RET, and VEGF receptors, which are involved in the pathogenesis of thyroid cancers, offering a strong molecular rationale for the treatment of all thyroid cancer subtypes.

In this retrospective study, we have reported the activity and safety of sorafenib in a group of patients with any subtype of thyroid cancer involved in an off-label program of sorafenib for the treatment of metastatic thyroid carcinoma. We acknowledge that our study has important weaknesses, including its retrospective nature, the small sample size, and the lack of a control arm. Indeed, with this design, it is impossible to draw any definitive conclusions on the activity of sorafenib in patients with metastatic thyroid cancer, which can only be addressed by larger prospective randomized, placebo-controlled, clinical trials. Despite, we believe that one of the advantages of our trial is that the study population consisted of consecutive patients who had not been previously

selected under the strict inclusion criteria of prospective trials, so the data obtained reflect the clinical situation in some ways. Also, by including the first 34 consecutive patients, the risk of retrospectively selecting the cases with better outcomes and the possibility of underestimating the occurrence of adverse events and overestimating the drug's efficacy are reduced.

The data obtained in our study are consistent with the data obtained from previous studies with sorafenib and also with other TKIs in patients with DTC in which the PR rate has ranged from 6 to 49% (19% in this study), SD rates from 38 to 67% (50% in our study), and mPFS from 15 to 20 months (13.3 months in our study). However, certain discrepancies such as initially documented disease progression status are seen that are likely related to different inclusion criteria between studies (Table 4). More recently, results of a phase II trial of pazopanib on patients with metastatic, rapidly progressive, radioiodine-refractory DTC showed a PR in 18 out of 39 patients, yielding a RR of 49% (95% CI: 35–68) (Bible *et al.* 2010). Also, high RRs have been obtained in patients with DTC with newer compounds, including lenvatinib (E7080). In a phase II trial of lenvatinib by Sherman *et al.* (2011), confirmed PRs were observed in 29 of the 58 patients, yielding a RR of 50% (95% CI: 37–63), and median PFS was 12.6 months (95% CI: 10.4–14.1), similar to the PFS obtained in our study (13.3 months). A multicenter, randomized, double-blind, placebo-controlled, phase III trial is currently recruiting participants (NCT01321554). This trial is allowing the inclusion

Figure 2 Median overall survival curves. Statistically significant differences were observed between DTC and anaplastic and also between MTC and anaplastic. No differences were observed between DTC and MTC.

Table 3 Main side effects ($n=34$)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hand-foot syndrome	7 (20)	6 (18)	7 (20)	1 (3)
Stomatitis	6 (18)	9 (26)	1 (3)	
Diarrheas	6 (18)	10 (29)	5 (15)	
Alopecia	3 (9)	2 (6)	4 (12)	
Hypertension	4 (12)	2 (12)		
Abdominal pain	5 (15)	5 (15)	1 (3)	
Rash	8 (23)	2 (6)	2 (6)	
Dry mouth	1 (3)	1 (3)		
Fatigue	8 (23)	6 (18)	5 (15)	
Anorexia	1 (3)	3 (9)	3 (9)	
Xerosis	9 (26)	1 (3)	1 (3)	
Dysgeusia	1 (3)			
Arthromyalgia	1 (3)			
Elevated transaminases			1 (3)	1 (3)

of patients that have received 0 or 1 before TKI, such as sorafenib, sunitinib, or pazopanib.

In a randomized, double-blind trial by Leboulleux *et al.*, 145 patients with locally advanced or metastatic DTC were randomized to vandetanib ($n=72$) or placebo ($n=73$). Compared with placebo, vandetanib significantly improved PFS (11.0 vs 5.8 months; hazard ratio: 0.63; 95% CI: 0.43–0.92; $P=0.008$), which is similar to the PFS obtained in our study (13.3 months) (Leboulleux *et al.* 2010).

Currently, there is ongoing discussion about the best criteria to evaluate antitumor activity of targeted therapies, and it seems that RECIST criteria do not properly evaluate all the real benefits of new targeted agents in solid tumors. We chose RECIST v1.0 criteria instead of RECIST v1.1 criteria in an attempt to assess the maximum number of target lesions in the same organ. This contrasts with RECIST v1.1 criteria, which reduces the number of target lesions per organ and could subsequently jeopardize the best evaluation of a disease that usually metastasizes to one or two different organs with measurable disease (lymph nodes and lung) (Eisenhauer *et al.* 2009). The first international placebo-controlled phase III study with sorafenib in a population with DTC has recently completed its recruitment and will define the role of this TKI drug in the management of advanced radioiodine-refractory DTC (NCT00984282).

Data on sorafenib in MTC are limited compared with data on sorafenib in DTC. Other TKIs have demonstrated promising activity against MTC, such as cabozantinib (XL184), sunitinib, and motesanib (Table 4). Vandetanib, in particular, has recently received US Food and Drug Administration (FDA) approval for the treatment of advanced MTC after positive results from a placebo-controlled phase III study, which demonstrated a significant benefit in mPFS (hazard ratio: 0.46; 95% CI: 0.31–0.69;

Table 4 Main studies in advanced thyroid cancer with targeted therapies

References	Drug	<i>n</i>	Tumor type	Response rate (%)	Stable disease (%)	Median progression-free survival (months)
Kloos <i>et al.</i> (2009)	Sorafenib	41	DTC and ATC	15	56	15
Gupta-Abramson <i>et al.</i> (2008)	Sorafenib	30	DTC	23	34	20
Hofstijzer <i>et al.</i> (2009)	Sorafenib	32	DTC	25	34	13.4
Ahmed <i>et al.</i> (2011)	Sorafenib	26	DTC and MTC	18 ^a	82	NR
Sherman <i>et al.</i> (2008)	Motesanib	93	DTC	14	67	9.2
Cohen <i>et al.</i> (2008)	Axitinib	60	All	30	38	18.1
Ravaud <i>et al.</i> (2008)	Sunitinib	17	All	30	38	NR
Carr <i>et al.</i> (2009)	Sunitinib	33	DTC and MTC	32	48	NR
Bible <i>et al.</i> (2010)	Pazopanib	37	DTC	49	NR	11.7
Leboulleux <i>et al.</i> (2010)	Vandetanib	145	DTC	8.3	56.9 ^b	11
Sherman <i>et al.</i> (2011)	Lenvatinib	58	DTC	59	36	13.3
De Souza <i>et al.</i> (2010)	Sunitinib	25	MTC	33	54	12
Kurzrock <i>et al.</i> (2010)	XL-184	37	MTC	29	41	NR
Wells <i>et al.</i> (2010)	Vandetanib/ placebo ^c	331	MTC	45	NR	19.3 vs not reached
Lam <i>et al.</i> (2010)	Sorafenib	21	MTC	6.3	87.5	17.9
Schlumberger <i>et al.</i> (2009)	Motesanib	91	MTC	2	81	11.1

ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; NR, not reported.

^a3-Month median follow-up.

^bDisease control rate.

^cPhase III study.

$P < 0.001$), objective RR ($P < 0.001$), and disease control rate ($P = 0.001$) (Wells et al. 2011).

Cabozantinib has also shown promising activity in a phase I dose escalation study carried out by Kurzrock et al. (2011). In this trial, ten out of 37 patients (29%) with MTC obtained a PR. Moreover, preliminary results of the ongoing EXAM (Efficacy of cabozantinib (XL184) in Advanced Medullary Thyroid Cancer) trial (NCT00704730) have been reported (<http://www.exelixis.com/pipeline/xl184>), which show that cabozantinib produces a significant 2.8-fold increase in PFS compared with placebo (11.2 vs 4.0 months; hazard ratio: 0.28; 95% CI: 0.19, 0.40; $P < 0.0001$).

The few data available on sorafenib in MTC patients showed limited activity with PR rates $< 10\%$ but higher SD rates especially in subgroup analyses of patients with tumor progression before study entry (Lam et al. 2010). Our data support the efficacy of sorafenib in a population of patients with MTC, achieving similar results compared with other TKIs in this setting (Table 4). Although trials are not directly comparable, it seems that different TKIs are able to provide significant benefit in MTC patients regardless of their affinity for wild-type or mutant RET receptors.

In ATC patients, the small sample number ($n = 3$) makes it difficult to extrapolate the data obtained from PR or SD. The observed results support a hypothesis of possible activity of TKIs in ATC. However, as some TKIs may need time to achieve active plasma concentrations to reduce tumor angiogenesis, these small molecules may not act as rapidly as necessary, and hence their use in ATC should be considered carefully.

The toxicity profile observed in this unselected cohort of patients was similar to that observed in previous studies and was managed mainly with both symptomatic treatment and sorafenib dose delay or reduction (35% in this study). It is of particular use to report the safety profile observed in routine clinical thyroid cancer patients, as toxicity data reported in patients in prospective clinical studies are often not taken from a representative sample. Although few patients presented grade 3–4-related toxicity, most patients presented some grade 1–2 side effects. For some of them, previously asymptomatic, this may represent a worsening in their quality of life that could jeopardize compliance to the treatment. Quality of life assessment is strongly recommended for future regulatory clinical trials.

With regard to tumor markers and their role in the evaluation of clinical efficacy, we observed that a reduction in CEA/calcitonin and thyroglobulin higher than 50% was correlated with PR. When we analyzed

the data by tumor subtype and tumor marker type, the results were not significant due to the small number of patients. Data in this area are conflicting in phase II clinical trials and our results only suggest possible predictive biomarkers for tumor response. These results need to be confirmed in large prospective phase III clinical trials and should also provide information on the time to achieve marker response (not available in our study) in order to recognize, within a few weeks, those patients who are less likely to obtain objective response, which would shorten unnecessary drug exposure.

In summary, we report the efficacy and toxicity profile of sorafenib used off-label for the treatment of advanced and refractory thyroid cancer in an unselected population representative of routine clinical practice. The observed efficacy data are comparable to other published studies with sorafenib in DTC patients. However, we report a cohort of patients with MTC with interesting clinical activity warranting further development in this setting.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

J Capdevila and J Tabernero involved in the conception and design of the study. J Capdevila, L Iglesias, I Halperin, Á Segura, J Martínez-Trufero, M Á Vaz, J Corral, G Obiols, E Grande, and J J Grau provided the study materials and recruited the patients. J Capdevila and E Grande collected and assembled the data. All the authors analyzed and interpreted the data. All the authors involved in writing the manuscript and approved the final manuscript.

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References

- Ahmed M, Barbachano Y, Riddell A, Hickey J, Newbold KL, Viros A, Harrington KJ, Marais R & Nutting CM 2011 Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: a phase II study in a UK based population. *European Journal of Endocrinology* **165** 315–322. (doi:10.1530/EJE-11-0129)
- Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, Rubin J, Sideras K, Morris JC III, McIver B *et al.* 2010 Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncology* **11** 962–972. (doi:10.1016/S1470-2045(10)70203-5)
- Carr L, Goulart B, Martins R, Keith E, Kell E, Wallace S, Capell P & Mankoff D 2009 Phase II trial of continuous dosing of sunitinib in advanced, FDG-PET avid, medullary thyroid carcinoma (MTC) and well-differentiated thyroid cancer (WDTC). *ASCO Meeting Abstracts* **27** 6056.
- Cohen EE, Rosen LS, Vokes EE, Kies MS, Forastiere AA, Worden FP, Kane MA, Sherman E, Kim S, Bycott P *et al.* 2008 Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *Journal of Clinical Oncology* **26** 4708–4713. (doi:10.1200/JCO.2007.15.9566)
- De Souza JA, Busaidy N, Zimrin A, Seiwert TY, Villaflor VM, Poluru KB, Reddy PL, Nam J, Vokes EE & Cohen EE 2010 Phase II trial of sunitinib in medullary thyroid cancer (MTC). *Proceedings of the American Society of Clinical Oncology* **28** 5504.
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M *et al.* 2009 New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer* **45** 228–247. (doi:10.1016/j.ejca.2008.10.026)
- Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, Mandel SJ, Flaherty KT, Loevner LA, O'Dwyer PJ *et al.* 2008 Phase II trial of sorafenib in advanced thyroid cancer. *Journal of Clinical Oncology* **26** 4714–4719. (doi:10.1200/JCO.2008.16.3279)
- Hoftijzer H, Heemstra KA, Morreau H, Stokkel MP, Corssmit EP, Gelderblom H, Weijers K, Pereira AM, Huijberts M, Kapiteijn E *et al.* 2009 Beneficial effects of sorafenib on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma. *European Journal of Endocrinology* **161** 923–931. (doi:10.1530/EJE-09-0702)
- Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, Liang J, Wakely PE Jr, Vasko VV, Saji M *et al.* 2009 Phase II trial of sorafenib in metastatic thyroid cancer. *Journal of Clinical Oncology* **27** 1675–1684. (doi:10.1200/JCO.2008.18.2717)
- Kurzrock R, Cohen EE, Sherman SI, Pfister DG, Cohen RB, Ball D, Hong DS, Ng CS, Salgia R & Ratain MJ 2010 Long-term results in a cohort of medullary thyroid cancer (MTC) patients (pts) in a phase I study of XL184 (BMS 907351), an oral inhibitor of MET, VEGFR2, and RET. *ASCO Meeting Abstracts* **28** 5502.
- Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, Cohen EE, Janisch L, Nauling F *et al.* 2011 Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *Journal of Clinical Oncology* **29** 2660–2666. (doi:10.1200/JCO.2010.32.4145)
- Lam ET, Ringel MD, Kloos RT, Prior TW, Knopp MV, Liang J, Sammet S, Hall NC, Wakely PE Jr, Vasko VV *et al.* 2010 Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. *Journal of Clinical Oncology* **28** 2323–2330. (doi:10.1200/JCO.2009.25.0068)
- Leboulleux S, Bastholt L, Krause TM, De La Fouchardiere C, Tennvall J, Awada A, Gómez JM, Tisseron-Carrasco A, Licour M & Schlumberger MJ 2010 Vandetanib in locally advanced or metastatic differentiated thyroid cancer (papillary or follicular; DTC): a randomized, double-blind phase II trial. *Annals of Oncology (ESMO Meeting Abstracts)* **21** viii314–viii328.
- Nikiforova MN & Nikiforov YE 2008 Molecular genetics of thyroid cancer: implications for diagnosis, treatment and prognosis. *Expert Review of Molecular Diagnostics* **8** 83–95. (doi:10.1586/14737159.8.1.83)
- Puxeddu E, Romagnoli S & Dottorini ME 2011 Targeted therapies for advanced thyroid cancer. *Current Opinion in Oncology* **23** 13–21. (doi:10.1097/CCO.0b013e328340cf94)
- Ravaud A, de la Fouchardiere C, Courbon F, Asselineau J, Klein M, Nicoli-Sire P, Bournaud C, Delord J, Weryha G & Catargi B 2008 Sunitinib in patients with refractory advanced thyroid cancer: the THYSU phase II trial. *ASCO Meeting Abstracts* **26** 6058.
- Schlumberger MJ, Elisei R, Bastholt L, Wirth LJ, Martins RG, Locati LD, Jarzab B, Pacini F, Daumerie C, Droz JP *et al.* 2009 Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer. *Journal of Clinical Oncology* **27** 3794–3801. (doi:10.1200/JCO.2008.18.7815)
- Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, Licitra L, Eschenberg MJ, Sun YN, Juan T *et al.* 2008 Motesanib diphosphate in progressive differentiated thyroid cancer. *New England Journal of Medicine* **359** 31–42. (doi:10.1056/NEJMoa075853)
- Sherman SI, Jarzab B, Cabanillas ME, Licitra LF, Pacini F, Martins R, Robinson B, Ball D, McCaffrey J, Shah MH *et al.* 2011 A phase II trial of the multi-targeted kinase inhibitor, lenvatinib (E7080), in advanced radioiodine (RAI)-refractory differentiated thyroid cancer (DTC). *ASCO Meeting Abstracts* **29** 5503.
- Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC *et al.* 2000 New guidelines to

- evaluate the response to treatment in solid tumors. *Journal of the National Cancer Institute* **92** 205–216. (doi:10.1093/jnci/92.3.205)
- Wells SA Jr, Gosnell JE, Gagel RF, Moley J, Pfister D, Sosa JA, Skinner M, Krebs A, Vasselli J & Schlumberger M 2010 Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *Journal of Clinical Oncology* **28** 767–772. (doi:10.1200/JCO.2009.23.6604)
- Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR *et al.* 2011 Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *Journal of Clinical Oncology* **30** 134–141. (doi:10.1200/JCO.2011.35.5040)
- Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M *et al.* 2004 BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Research* **64** 7099–7109. (doi:10.1158/0008-5472.CAN-04-1443)
- Yu XM, Lo CY, Chan WF, Lam KY, Leung P & Luk JM 2005 Increased expression of vascular endothelial growth factor C in papillary thyroid carcinoma correlates with cervical lymph node metastases. *Clinical Cancer Research* **11** 8063–8069. (doi:10.1158/1078-0432.CCR-05-0646)

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