



## EDITORIAL

### Use of new molecules in the treatment of advanced thyroid cancer<sup>☆</sup>

### Uso de nuevas moléculas en el tratamiento del cáncer avanzado de tiroides

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At the beginning of the 20th century, thyroid cancer (TC) was poorly known and had a gloomy prognosis. At that time, Emile Theodor Kocher, thanks to his surgical experience, was awarded the Nobel prize for Medicine (1909) for his contribution to understanding and cure of pathological thyroid

conditions. However, progress in this field was slow. Twenty-two years later, in 1931 (i.e. 80 years ago), Clute,<sup>1</sup> a surgeon also, published in *The New England Journal of Medicine* one of the first clinical observations of aspects related to TC. Clute classified the disease into 3 groups based on histological appearance and prognosis. In group I, which would correspond to what is now called stage I and II differentiated thyroid carcinoma (DTC), Clute found a 5% mortality rate. Group II consisted of DTCs with significant local invasion (which would now be classified as stage III). The mortality rate in this group was 24%. These patients (groups I and II) were recommended surgery and subsequent radiotherapy,

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which maintained patients free of disease for an average of 3 years. Finally, group III consisted of the most aggressive tumors (probably anaplastic or poorly differentiated carcinomas that would now be classified as stage IV), for which neither surgery nor radiotherapy were curative. The mortality rate was as high as 82%, and patients died within a few months. In the article, Clute<sup>1</sup> stated: *Since there is so little that we can do for patients in this condition, either in the way of palliative or curative measures, it is but natural that for many years the general feeling amongst medical men has been that malignancy arising in the thyroid was an utterly hopeless condition which, fortunately, was usually of but short duration.* And things continued to be so for over two decades.

The next qualitative advance which improved surgical results was the advent, in the 1940s, of treatment with radioactive iodine (<sup>131</sup>I). <sup>131</sup>I raised the survival rate of patients with lung diseases from 25% to 75% at 10 years.<sup>2</sup> With this therapeutic armature (scalpel and <sup>131</sup>I), the cure rate approached 90–95%. Since TC affects an endocrine gland (with its attendant unique characteristics) and usually has a good prognosis, its treatment naturally fell into the hands of endocrinologists. Endocrinologists have diagnosed TC and have coordinated the work of the different specialists involved in its treatment from the start. After initial treatment, endocrinologists have also monitored these patients for the occurrence of relapse. TC management has been particularly critical in the small proportion of patients (5–10%) in whom the forecast of Clute has become a reality. These are patients with advanced, progressive TC (ATC) with metastases resistant to <sup>131</sup>I, who are not amenable to surgery.

Several attempts were made over time to use additional therapeutic measures in this group of patients with ATC. From 1975 to 1999, 15 clinical trials using cytotoxic chemotherapy were started in these patients. None of these trials was able to recruit the planned number of patients, and only 5 trials reported their results, which were discouraging.<sup>3</sup> Treatment with doxorubicin and cisplatin achieved complete remission in only 12% of patients with ATC of a follicular origin. The combination of bleomycin, doxorubicin, and cisplatin achieved a mean survival of 11 months, and response to etoposide was nil. There was a similar occurrence in patients with ATC of a medullary origin, only 25% of whom showed partial or complete response to treatment.<sup>4</sup> This is why oncologists, amongst others, lost interest in this malignancy, which showed a unique behavior. At the turn of the 20th century, in 2000, therapeutic solutions available for patients with ATC were virtually nonexistent.

Fortunately, the situation is quite different today, and we are witnessing a new qualitative leap in the treatment of TC. Dramatic advances in molecular medicine in recent years have opened up new therapeutic possibilities.<sup>5,6</sup> Such advances have gradually disclosed some of the mechanisms by which thyroids cells become malignant. The role of the membrane receptors RET/PTC, EGFR, and C-MET in DTC is now known. The occurrence of signaling defects in tumor cells has also been traced in both the RAS-PI3K-AKT and BRAF-MEK-ERK pathways. Thorough research has been made on the significance of the V600E mutation of BRAF, which usually occurs in the most aggressive variants of papillary

carcinoma (PC) or is related to epigenetic changes.<sup>7,8</sup> There have been advances in both follicular and medullary (MC) DTC.

Parallel discoveries have also improved our understanding of the molecular mechanisms implicated in the development of many other more prevalent cancers. Based on such advances, the pharmaceutical industry has started to develop what have generically been called “novel molecules” for the treatment of malignant diseases. Such “novel molecules” have as common characteristics their actions against one or several molecular targets, their oral administration (usually in daily schemes), and less harmful side effects than those usually induced by chemotherapy. Most of these new molecules are multikinase inhibitors with diverse actions which interact (selectively or as a group) with various proteins such as RET, BRAF, cKIT, MET, EGFR, MAPK, PDGFR $\beta$ , etc.<sup>3,5,6</sup> They also have the added advantage that they markedly inhibit angiogenesis by acting upon VEGFR-1, 2, and 3.<sup>5</sup>

As noted, these compounds (like most drugs) are not free from side effects, but these may rapidly be detected by routine monitoring of these patients and may usually be managed on an outpatient basis.<sup>6,9</sup> Common side effects reported include weakness, high blood pressure, gastrointestinal discomfort (abdominal pain diarrhea, constipation, vomiting, and anorexia), skin lesions (palmar-plantar erythrodysesthesia or hand-foot syndrome), or fatigue.<sup>6,10</sup> Patients may also report hand and feet paresthesia, hypopigmentation, dizziness, blurred vision, altered taste, or flu-like symptoms. Anemia, leukopenia, or a decreased platelet count, with an increased risk of bleeding, has also been reported.<sup>11</sup> Changes in liver or kidney function tests, electrolyte changes, or severe bleeding are rare occurrences (in less than 10% of patients).<sup>12</sup> Adverse effects are usually dose-dependent, and therefore tend to be resolved when the drug is temporarily suspended or its dose is reduced.<sup>6,12</sup>

Of special interest, particularly in the setting of TC, is the fact that the use of tyrosine kinase inhibitors has been associated with the occurrence of thyroid dysfunction.<sup>13–15</sup> This effect has especially occurred following the administration of sunitinib and sorafenib.<sup>16,17</sup> The most common dysfunction is the development of hypothyroidism, which has sometimes been reported after a short episode of thyrotoxicosis (mimicking the clinical phases of thyroiditis). Athyroid patients usually require on average a 30% increase in L-thyroxine dose either to maintain the suppression of TSH levels or to preserve a euthyroid state.<sup>18</sup> There has been speculation that these compounds may trigger some destructive mechanism in the thyroid gland or interact with TSH signaling pathways, because these drugs increase T<sub>4</sub> and T<sub>3</sub> metabolism, probably through the induction of type 3 deiodinase.<sup>14,19</sup> Careful and frequent thyroid function monitoring is therefore advised in any patient treated with these molecules.<sup>20</sup>

Because of their role as coordinators of TC patient management, some endocrinologists started to include patients with ATC in clinical trials of the new molecules (as noted above, there were virtually no therapeutic possibilities available for these patients). The first drug tested was motesanib, a multikinase inhibitor (RET, PDGFR $\beta$ , FLT3, and cKIT, VEGFR-1, 2 and 3). In 2005, Rosen et al.<sup>21</sup> reported at

the meeting of the *American Society of Clinical Oncology* (ASCO) the results of a Phase I clinical trial of motesanib in 70 patients with solid tumors. Ten percent of these patients had ATC in which conventional treatment had failed. One year later, Boughton et al.<sup>22</sup> specifically addressed the same meeting on the effect of motesanib on this subgroup of 7 patients with ATC. By a fortunate stroke of luck, the histology of these tumors was diverse: there were 3 PCs, one follicular carcinoma (FC), one Hürthle cell carcinoma, one anaplastic carcinoma (AC), and one MC. Encouraging results were found: partial response was achieved in 3 patients (one each with PC, FC, and MC), the disease stabilized in another 3 patients, and disease progression occurred in the remaining patient. These data led to 2 Phase II clinical trials with motesanib being started, one on patients with differentiated ATC and the other on patients with MC. The attractiveness of the proposal was shown by the fact that 93 patients (13 more than those initially planned) were recruited within a short time for the trial in differentiated ATC. In 2008, Sherman et al.<sup>23</sup> reported the results of the international, multicenter trial. The report showed that the disease stabilized in 67% of patients, and the effect was maintained for a mean of 24 weeks (or longer) in 35% of them. Results also appeared to suggest that the clinical benefit was greater in patients with BRAF mutations (33% versus 60%), but the number of patients in whom the mutation was studied was small, and this finding did not therefore reach statistical significance. The results of the trial in MC patients were disclosed a few months later.<sup>24</sup> Overall, lower antitumor activity was seen in the latter patients, which was related to probable pharmacokinetic differences for reasons which are not well understood yet.

These results acted as an incentive for both endocrinologists and oncologists, as is shown by the following data. From 2000 to 2005, a mean of 2.8 papers presented at annual ASCO meetings contained in their title the words "thyroid cancer". From 2006 to date, such mean has substantially increased to 10.0 papers per ASCO meeting. This figure is however much lower as compared to the numbers of papers submitted by oncologists on other malignancies such as lung (293 papers to the 2011 ASCO meeting<sup>25</sup>), breast (653), lymphoma (125), or melanoma (113). In 2011, 11 papers on thyroid cancer were presented at ASCO. As a comparison, 705 papers containing the term "thyroid cancer" were submitted to the 2011 meeting of the Endocrine Society.<sup>26</sup>

After the motesanib trials, other similar studies were conducted in both differentiated ATC and medullary carcinoma with similar results. New molecules are being administered to patients with ATC virtually as soon as they appear on the therapeutic horizon. The results of other trials with imatinib,<sup>27</sup> axitinib,<sup>28</sup> sorafenib,<sup>12,29</sup> AZD6244,<sup>30</sup> gefitinib,<sup>31</sup> tipifarnib,<sup>32</sup> vandetanib,<sup>33</sup> sunitinib,<sup>34–36</sup> and more recently pazopanib,<sup>37</sup> cabozantinib (XL184),<sup>38</sup> and lenvatinib (E7080)<sup>39</sup> were soon reported. As the result of ongoing research in melanoma, PC is starting to be treated with specific BRAF inhibitors.<sup>8,40–42</sup> An example of such treatment is a Phase I trial with PLX4032 (a specific inhibitor of the kinase activity of mutated BRAF protein in V600E) in which encouraging preliminary results have been found in 3 patients with PC.<sup>43,44</sup> PLX4032 does not alter

kinase activity of the wild type, or nonmutated, protein. This decreases the risk of adverse effects derived from the inhibition of kinases in other tissues. Because of the good results found in melanoma and since V600E BRAF is markedly prevalent in aggressive PCs, PLX4032 may be a promising treatment in the future. In fact, a Phase II trial of this compound which will recruit patients with PC having the V600E mutation in BRAF has already been approved.

The pooled information of the results of the clinical trials shows that these new molecules achieve partial remission in 20–30% of patients, and that the disease stabilizes in 70–90% of patients. No complete remissions have been reported yet. However, a comparison of the efficacy of the different drugs shows variable results. Thus, for example, treatment with gefitinib provided no benefit to patients with ATC.<sup>31</sup> It has also been reported that there are patients resistant to a molecule who show, however, a positive response when treated with another drug.<sup>45</sup> Such diversity in behavior is probably due to the existence of multiple activation mechanisms and to the specificity of each compound to correct a limited number of specific mutations, while it has no activity against others.<sup>46</sup> Gene activation cascades have pleomorphic characteristics and, by definition, neoplastic cells have a heterogeneous basis. Mutations may also occur in both parenchyma or stroma and in endothelial cells supporting the tumor.<sup>44</sup> It should also be noted that there are added factors, such as individual variation, that condition diversity in pharmacokinetics. Overall, these findings have led to clinical trials with combined treatments being designed and to the consideration that the therapeutic failure of a specific molecule in one patient does not necessarily rule out its recruitment into another clinical trial with a different compound.<sup>32,47,48</sup>

Many clinical trials are currently ongoing with these molecules in patients with ATC. A good part of them are actively recruiting patients, while others have already been closed and their results are being analyzed. Their current status, the sites where they are being conducted, and their conditions may be consulted at <http://www.cancer.gov/clinicaltrials/> or <http://clinicaltrials.gov/>. Most of these are Phase II trials, while others have already evolved to the next phase because of the good results achieved. This is the case of sorafenib, which is being tested in a Phase III trial where patient recruitment has recently been completed. This is a multicenter, international trial in which approximately 400 patients with ATC (excluding MC) have been recruited and in which several Spanish sites have participated. Phase III clinical trials with vandetanib<sup>45</sup> and cabozantinib<sup>38</sup> in patients with MC are also being conducted, amongst others. Unlike with clinical trials with cytotoxic chemotherapy, the results are being reported and published even before the studies are closed. All of this suggests that the use of the new molecules for the treatment of ATC will be approved and will be a part of standard clinical practice within a short time. We believe that specialists who coordinate TC treatment should be prepared for this eventuality.

The recent thyroid cancer guidelines issued by the *American Thyroid Association* (ATA) recommend the use of treatments with new molecules in patients with ATC.<sup>49,50</sup> Because of this and the historical background we have just summarized, we believe that endocrinologists should familiarize themselves with the scope and limitations of the new

molecules in order to be able to adequately decide when they should be introduced into treatment. They should also know how to manage the side effects of such molecules, especially as some of them, such as hypothyroidism, directly affect the course of TC patients.<sup>51,52</sup> Endocrinologists are specialists who have a privileged overall view of patients with TC, and are also the specialists involved in the integral management of the condition from diagnosis to the end of the disease. This means that endocrinologists must have their offices open to any patient with TC regardless of disease prognosis or stage. In the same way as endocrinologists would not leave patients with TC with a satisfactory course in the hands of other specialists, we think that it would be a mistake to give up the care of patients with a poor prognosis or to refer them to another physician merely out of convenience. An endocrinologist who adopted a passive stance towards his or her patients in the most advanced stages of ATC would lower the competence of the specialty, and such an attitude would ultimately be to the detriment of all patients. In this regard, we have been surprised by the position statement by Spanish oncologists (SEOM) that advocates for themselves the exclusive use of these new oral agents. This is hardly compatible with the basic harmony we think should exist between the different medical and surgical specialties to the benefit of our patients.<sup>53</sup> We think that, just as it would be unreasonable that we endocrinologists claimed for ourselves the exclusive use of any hormone drug (glucocorticoids, insulin, mineralocorticoid inhibitors, etc.), since we understand that they are needed by many diverse specialists who are fully qualified to use them, so it would be unfair to consider that any given specialty has an exclusive right to the use of any class of drugs.

To sum up, the complexity of the management of TC patients requires the intervention of physicians from various specialties. Adequate diagnosis depends to a great extent on cytologists, and reports from radiologists are often decisive. Initial treatment not only consists of tumor resection by the surgeon or otolaryngologist, but also of patient assessment by the specialist in nuclear medicine to weigh the need for administering <sup>131</sup>I. The skills of the pathologist who analyzes the surgical specimen from both the morphological and the (increasingly necessary) molecular viewpoints are also essential. The clinical laboratory plays a key role in monitoring, by providing accurate measurements of levels of thyroglobulin, its antibodies, and thyroid hormones. Because of their experience in the management of hormone treatments, endocrinologists are well qualified to calculate the dose of L-thyroxine appropriate after thyroidectomy according to the histological types and variants, as well as TC origin, the evolutive stage of the disease, and patient condition, by starting either suppressive or replacement therapy. Endocrinologists also adjust hormone dosage to different conditions such as pregnancy or patient age, and take into account any potential drug interactions with concomitant treatments. During follow up, a proportion of patients need repeat surgery or the qualified help provided by nuclear medicine, either to have disease extension assessed or new treatments administered. In selected cases, the collaboration of medical or radiotherapeutic oncology, or even surgical subspecialties such as neurosurgery, thoracic surgery, or orthopedic surgery should

be requested. This involves endocrinologists in wide-ranging coordination work. For this to be effective, endocrinologists caring for patients with TC have to cooperate with all kinds of specialists and be aware of the possibilities offered by each specialty. It is also indispensable for them to become familiar with these new prospects for improving the diagnosis, treatment, prognosis, and course of the disease which have been opened up by research in the different areas of medicine. It is easy to infer that in the not too distant future, treatments with new molecules will be implemented only after a specific diagnosis based on a molecular analysis of tumor tissue has been made in each patient. This will serve to determine the specific therapeutic targets that should be repaired with the most adequate drug. The intended objective is to implement individualized therapy specifically directed to the pathological target. This, it is predicted, will preserve the healthy cells while selectively killing only those that are diseased.

## References

1. Clute HM. Clinical aspects of thyroid malignancy. *N Engl J Med*. 1931;205:1083–5.
2. Ronga G, Filesi M, Montesano T, Di Nicola AD, Pace C, Travascio L, et al. Lung metastases from differentiated thyroid carcinoma. A 40 years' experience. *Q J Nucl Med Mol Imaging*. 2004;48:12–9.
3. Sherman SI. Cytotoxic chemotherapy for differentiated thyroid carcinoma. *Clin Oncol*. 2010;22:464–8.
4. Vitale G, Caraglia M, Ciccarelli A, Lupoli G, Abbruzzese A, Tagliaferri P, et al. Current approaches and perspectives in the therapy of medullary thyroid carcinoma. *Cancer*. 2001;91:1797–808.
5. Riesco-Eizaguirre G, Santisteban P. New insights in thyroid follicular cell biology and its impact in thyroid cancer therapy. *Endocr Relat Cancer*. 2007;957–77.
6. Sherman SI. Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers. *J Clin Endocrinol Metab*. 2009;94:1493–9.
7. Riesco-Eizaguirre G, Gutiérrez-Martínez P, García-Cabezas MA, Nistal M, Santisteban P. The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na<sup>+</sup>/I<sup>-</sup> targeting to the membrane. *Endocr Relat Cancer*. 2006;13:257–69.
8. Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. *Endocr Rev*. 2007;28:742–62.
9. Brassard M, Neraud B, Trabado S, Salenave S, Brailly-Tabard S, Borget I, et al. Endocrine effects of the tyrosine kinase inhibitor vandetanib in patients treated for thyroid cancer. *J Clin Endocrinol Metab*. 2011 [Epub ahead of print].
10. Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol*. 2009;27:1675–84.
11. Gkountouvas A, Kostoglou-Athanassiou I, Veniou E, Repousis P, Ziras N, Kaldrimidis P. Hematologic toxicity in patients treated with sunitinib for advanced thyroid cancer. *Thyroid*. 2010;20:597–600.
12. Gupta-Abramson V, Troxel AB, Nellore A, Puttaswamy K, Redlinger M, Ransone K, et al. Phase II trial of sorafenib in advanced thyroid cancer. *J Clin Oncol*. 2008;26:4714–9.
13. Grossmann M, Premaratne E, Desai J, Davis ID. Thyrotoxicosis during sunitinib treatment for renal cell carcinoma. *Clin Endocrinol (Oxf)*. 2008;69:669–72.

14. Illouz F, Laboureaux-Soares S, Dubois S, Rohmer V, Rodien P. Tyrosine kinase inhibitors and modifications of thyroid function tests: a review. *Eur J Endocrinol.* 2009;160:331–6.
15. Pfister DG, Fagin JA. Refractory thyroid cancer: a paradigm shift in treatment is not far off. *J Clin Oncol.* 2008;26:4701–4.
16. Wolter P, Stefan C, Decallonne B, Dumez H, Bex M, Carmeliet P, et al. The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. *Br J Cancer.* 2008;99:448–54.
17. Salem AK, Fenton MS, Marion KM, Hershman JM. Effect of sunitinib on growth and function of FRTL-5 thyroid cells. *Thyroid.* 2008;18:631–5.
18. Sherman SI. Early clinical studies of novel therapies for thyroid cancers. *Endocrinol Metab Clin North Am.* 2008;37:511–24.
19. Abdulrahman RM, Verloop H, Hoftijzer H, Verburg E, Hovens GC, Corssmit EP, et al. Sorafenib-induced hypothyroidism is associated with increased type 3 deiodination. *J Clin Endocrinol Metab.* 2010;95:3758–62.
20. Schlumberger M, Sherman SI. Clinical trials for progressive differentiated thyroid cancer: patient selection, study design, and recent advances. *Thyroid.* 2009;19:1393–400.
21. Rosen L, Kurzrock R, Jackson E, Wathen L, Parson M, Eschenberg M, et al. Safety and pharmacokinetics of AMG 706 in patients with advanced solid tumors. *J Clin Oncol.* 2005;23:165.
22. Boughton D, Rosen L, Van Vugt A, Kurzrock R, Eschenberg M, Wiezorek J, et al. Safety and antitumor activity of AMG 706 in patients with thyroid cancer: A subset analysis from a phase 1 dose-finding study. *J Clin Oncol.* 2006;24:185.
23. Sherman SI, Wirth LJ, Droz JP, Hofmann M, Bastholt L, Martins RG, et al. Motesanib diphosphate in progressive differentiated thyroid cancer. *N Engl J Med.* 2008;359:31–42.
24. Schlumberger MJ, Elisei R, Bastholt L, Wirth LJ, Martins RG, Locati LD, et al. Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer. *J Clin Oncol.* 2009;27:3794–801.
25. [http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst\\_meeting\\_categories.view&confID=102](http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_meeting_categories.view&confID=102).
26. <http://edrv.endojournals.org/content/vol32/03.Meeting-Abstracts/>.
27. de Groot JW, Zonnenberg BA, van Ufford-Mannesse PQ, de Vries MM, Links TP, Lips CJ, et al. A phase II trial of imatinib therapy for metastatic medullary thyroid carcinoma. *J Clin Endocrinol Metab.* 2007;92:3466–9.
28. Cohen EE, Rosen LS, Vokes EE, Kies MS, Forastiere AA, Worden FP, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. *J Clin Oncol.* 2008;26:4708–13.
29. Keefe SM, Troxel AB, Rhee S, Puttaswamy K, O'Dwyer PJ, Loevner LA, et al. Phase II trial of sorafenib in patients with advanced thyroid cancer. *J Clin Oncol.* 2011;29 Suppl [abstract 5562].
30. Adjei AA, Cohen RB, Franklin W, Morris C, Wilson D, Molina JR, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. *J Clin Oncol.* 2008;26:2139–46.
31. Pennell NA, Daniels GH, Haddad RI, Ross DS, Evans T, Wirth LJ, et al. A phase II study of gefitinib in patients with advanced thyroid cancer. *Thyroid.* 2008;18:317–23.
32. Hong DS, Sebti SM, Newman RA, Blaskovich MA, Ye L, Gagel RF, et al. Phase I trial of a combination of the multikinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in advanced malignancies. *Clin Cancer Res.* 2009;15:7061–8.
33. Wells Jr SA, Gosnell JE, Gagel RF, Moley J, Pfister D, Sosa JA, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *J Clin Oncol.* 2010;28:767–72.
34. Cleary JM, Sadow PM, Randolph GW, Palmer EL, Lynch TP, Nikiforov YE, et al. Neoadjuvant treatment of unresectable medullary thyroid cancer with sunitinib. *J Clin Oncol.* 2010;28:e390–2.
35. Carr LL, Mankoff DA, Goulart BH, Eaton KD, Capell PT, Kell EM, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. *Clin Cancer Res.* 2010;16:5260–8.
36. Ravaud A, de la Fouchardière C, Asselineau J, Delord JP, Do Cao C, Niccoli P, et al. Efficacy of sunitinib in advanced medullary thyroid carcinoma: intermediate results of phase II THYSU. *Oncologist.* 2010;15:212–3.
37. Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, et al. Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. *Lancet Oncol.* 2010;11:962–72.
38. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, et al. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. *J Clin Oncol.* 2011;29:2660–6.
39. Sherman SI, Jarzab B, Cabanillas ME, Licitra LF, Pacini F, Martins R, et al. A phase II trial of the multitargeted kinase inhibitor E7080 in advanced radioiodine-refractory differentiated thyroid cancer. *J Clin Oncol.* 2011;29 Suppl [abstract 5503].
40. Nucera C, Lawler J, Parangi S. BRAF (V600E) and microenvironment in thyroid cancer: a functional link to drive cancer progression. *Cancer Res.* 2011;71:2417–22.
41. Salerno P, De Falco V, Tamburrino A, Nappi TC, Vecchio G, Schweppe RE, et al. Cytostatic activity of adenosine triphosphate-competitive kinase inhibitors in BRAF mutant thyroid carcinoma cells. *J Clin Endocrinol Metab.* 2010;95:450–5.
42. Zafón C, Obiols G. The mitogen-activated protein kinase (MAPK) signaling pathway in papillary thyroid cancer. From the molecular bases to clinical practice. *Endocrinol Nutr.* 2009;56:176–86.
43. Flaherty K, Puzanov I, Sosman J, Kim K, Ribas A, McArthur G, et al. Phase I study of PLX4032: proof of concept for V600E BRAF mutation as a therapeutic target in human cancer. *J Clin Oncol.* 2009;27 Suppl. 15 [abstract 9000].
44. Sherman SI. Targeted therapies for thyroid tumors. *Mod Pathol.* 2011;24 Suppl. 2:S44–52.
45. Sherman SI. Targeted therapy of thyroid cancer. *Biochem Pharmacol.* 2010;80:592–601.
46. Verbeek HH, Alves MM, de Groot JW, Osinga J, Plukker JT, Links TP, et al. The effects of four different tyrosine kinase inhibitors on medullary and papillary thyroid cancer cells. *J Clin Endocrinol Metab.* 2011;96:E991–5.
47. Hong DS, Cabanillas ME, Wheeler J, Naing A, Tsimberidou AM, Ye L, et al. Inhibition of the Ras/Raf/MEK/ERK and RET kinase pathways with the combination of the multikinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in medullary and differentiated thyroid malignancies. *J Clin Endocrinol Metab.* 2011;96:997–1005.
48. Sweeney CJ, Chiorean EG, Verschraegen CF, Lee FC, Jones S, Royce M, et al. A phase I study of sunitinib plus capecitabine in patients with advanced solid tumors. *J Clin Oncol.* 2010;28:4513–20.
49. Cooper DS, Doherty GD, Haugen BR, Kloos RT, Lee SL, Mandel SL, et al. Revised American Thyroid Association man-

- agement guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19:1167–214.
50. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19:565–612.
51. Lodish MB, Stratakis CA. Endocrine side effects of broad-acting kinase inhibitors. *Endocr Relat Cancer*. 2010;17:R233–44.
52. Ye L, Santarpia L, Gagel RF. The evolving field of tyrosine kinase inhibitors in the treatment of endocrine tumors. *Endocr Rev*. 2010;31:578–99.
53. Colomer R, Alba E, González-Martin A, Paz-Ares L, Martín M, et al. Treatment of cancer with oral drugs: a position statement by the Spanish Society of Medical Oncology (SEOM). *Ann Oncol*. 2010;21:195–8.