Beneficial effects of sorafenib on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma

Hendrieke Hoftijzer1, Karen A Heemstra1, Hans Morreau2, Marcel P Stokkel3, Eleonora P Corssmit1, Hans Gelderblom4, Karin Weijers2, Alberto M Pereira1, Maya Huijberts5, Ellen Kapiteijn4, Johannes A Romijn2 and Johannes W Smit1

Departments of 1Endocrinology and Metabolism, C4-R, 2Pathology, 3Nuclear Medicine and 4Oncology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands and 5Department of Endocrinology, Maastricht University Medical Center, Maastricht, The Netherlands

(Correspondence should be addressed to J W A Smit; Email: jwasmit@lumc.nl)

(H Hoftijzer and K A Heemstra contributed equally to this work)

Abstract

Objective: Treatment options for patients with radioactive iodine (RaI) refractory metastases of differentiated thyroid carcinoma (DTC) are limited. We studied the effects of the multitarget tyrosine kinase inhibitor sorafenib on the reinduction of RaI uptake and tumor progression.

Design: Open, single center, single arm 26-week prospective phase II study with open-ended extension.

Methods: We treated 31 patients with progressive metastatic or locally advanced RaI refractory DTC with sorafenib 400 mg b.i.d. The primary endpoint was reinduction of RaI uptake at 26 weeks. Additional endpoints were the radiological response and the influence of bone metastases.

Results: At 26 weeks of sorafenib therapy, no reinduction of RaI uptake at metastatic sites was observed, but 19 patients (59%) had a clinical beneficial response, eight of whom had a partial response (25%) and 11 had stable disease (34%). Seven patients had progressive disease (22%). Sorafenib was significantly less effective in patients with bone metastases. The estimated median progression free survival was 58 weeks (95% confidence interval, CI, 47–68). In general, thyroglobulin (Tg) response (both unstimulated and TSH stimulated) reflected radiological responses. The median time of the nadir of Tg levels was 3 months. Responses were not influenced by histological subtype, mutational status or other variables. No unusual side effects were observed.

Conclusions: Sorafenib has a beneficial effect on tumor progression in patients with metastatic DTC, but was less effective in patients with bone metastases. Diagnostic whole body scintigraphy did not reveal an effect of sorafenib on the reinduction of RaI uptake.

European Journal of Endocrinology 161 923–931

Introduction

The prognosis of differentiated thyroid carcinoma (DTC) in general is favorable due to the efficacy of the combined treatment of surgery and radioactive iodine (RaI) and the biological behavior of the tumor (1, 2). However, ~50% of patients with distant metastases of DTC die within 10 years of diagnosis (3). Although the role of RaI in recurrent or metastatic thyroid cancer is beyond dispute (4–6), the efficacy of this therapy is hampered by the decreased expression of the sodium iodide symporter (NIS) in DTC during the process of dedifferentiation (7–9). Predictive factors for responsiveness to RaI treatment include a younger age, small metastases, well-differentiated thyroid tumor histology and the absence of uptake of 18-fluoro deoxyglucose (FDG) at FDG-positron emission tomography (PET) scanning. Especially in patients with bone metastases, the efficacy of RaI is limited to 7–20% of the patients (4, 6, 10, 11). At present, there are no effective therapies available for RaI non-avid DTC. Conventional chemotherapy is hardly effective in DTC, and no longer recommended in international guidelines (12, 13).

In DTC, many genetic alterations have been identified, involving tyrosine kinase signaling pathways (14–16). In nearly all cases of papillary thyroid carcinoma (PTC), genetic defects involving the RET, RAS, and RAF protein kinase signaling cascade are identified. The BrafV600E mutation has been found in 29–69% of PTC and has been associated with aggressive features including extrathyroidal extension and advanced stage (17). Translocations of RET observed in PTC result in a chimeric protein consisting of an activated RET tyrosine kinase domain (15, 18–32). Follicular thyroid carcinomas (FTC) frequently harbor mutations in one of the three RAS genes.
The RET–RAS–RAF pathway is interconnected with the epithelial growth factor receptor (EGFR) activated cascade that among others leads to vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) synthesis. Therefore, compounds targeting the activated RET–RAS–RAF pathway and beyond may be effective in non-RaI avid DTC. The anti-EGFR compound gefitinib was not successful in 27 patients with DTC, medullary or anaplastic thyroid carcinoma (33). In a phase II study in 60 thyroid carcinoma patients with various histologies, the VEGFR inhibitor axitinib showed a partial response of 30% (median progression free survival (PFS) 18 months) (34). Recently, 3 phase II studies have been published, using multi-kinase inhibitors (35–37). Motesanib diphosphate induced a partial response in 14% of 93 DTC patients (median PFS 40 weeks) (36). Two studies have been published using sorafenib. Sorafenib (BAY 43-9006) is an inhibitor of RET, CRAF, wild-type and mutant (V600E) BRAF, VEGFR1, -2, -3, Flt3, and c-KIT.

In the first study, including DTC, anaplastic and medullary thyroid carcinoma patients, sorafenib induced a partial response in 23% (median PFS 79 weeks). In the second study, including patients with DTC and anaplastic thyroid carcinoma, a partial response was observed in 11% (median PFS 4.5–16 weeks) (37). As bone metastases of DTC are poorly responsive to RaI, the response of bone metastases to the above-mentioned therapies is of interest. However, there were no separate analyses for patients with bone metastases in the above-mentioned studies.

In DTC, a relationship has been identified between genetic alterations in the RET, RAS, RAF cascade and loss of NIS expression (17, 38). Interestingly, in an in vitro study, sunitinib was able to reinduce NIS expression in RET/PTC transformed thyroid cells (39). In addition, sunitinib also increased RaI uptake in FRTL-5 cells. We therefore hypothesized that treatment with a multiple kinase inhibitor not only reduces tumor progression, but may also restore RaI uptake in non-RaI avid DTC. Therefore, we performed a single arm phase II trial to determine the efficacy of sorafenib in patients with iodine-refractory metastatic DTC, focusing on the reinduction of RaI uptake and the efficacy in bone metastases.

**Patients and methods**

**Patients**

Eligibility criteria for the present study were the presence of progressive metastases or unresectable local recurrence of DTC for which RaI therapy was no longer effective, as indicated by prior negative post-therapeutic whole body scintigraphy (WBS). Progressive disease was defined according to response evaluation criteria in solid tumors (RECIST) criteria in the year before initiation of treatment. Patients who were selected, had to have undergone total thyroidectomy and RaI ablative therapy. Exclusion criteria were pregnancy, contraindications for the application of recombinant human thyrotropin (rhTSH) and contraindications for the use of sorafenib. In addition, no patients with poorly responsive DTCs were included as it was hypothesized that the likelihood of reinduction of RaI uptake in this category of tumors would be very small. Other eligibility criteria included Eastern Cooperative Oncology Group performance status 0–2 and life expectancy more than 3 months. Patients were ineligible if they had previous exposure to biological therapies. All patients provided written informed consent before enrollment onto the trial. The study protocol was approved by the Institutional Review Board of the Leiden University Medical Center. This study has been registered at ClinicalTrials.gov (#NCT00887107).

**Study design**

The study was a 26-week open-label, single-arm, phase II study of oral sorafenib in patients with metastatic DTC. The primary objective was to study the effect of sorafenib treatment on reinduction of radioiodine uptake. Secondary objectives were radiological tumor response according to RECIST and the relation between the presence of bone metastases and therapy success. Sorafenib was initially administered at a dose of 400 mg orally twice a day. Eligibility assessments, including a review of medical history and prior treatments, physical examination and laboratory assessments were completed within 2 weeks before initiation of the sorafenib therapy. Baseline radiological evaluation by computed tomography (CT) of target lesions was performed 4 weeks prior to initiation of therapy. From all patients, tumor samples from the primary tumors were obtained for review by the institutional pathologist (H M). After inclusion, the patients underwent a diagnostic scintigraphy 3 days after i.v. administration of 185 MBq I-131 (Mallinckrodt BV, Petten, The Netherlands). Single photon emission computed tomography (SPECT) of the head and neck and chest was performed. Two experienced observers visually analyzed all images. An I-131 standard was used to quantify the uptake in the area of interest at WBS. Patients were prescribed a low iodide diet from 7 days prior to the administration of I-131 (40). The patients received i.m. injections with 0.9 mg rhTSH (Thyrogen, Genzyme, Naarden, The Netherlands) on two consecutive days before the RaI administration. The day after the first WBS, patients started treatment with sorafenib 400 mg bid. Twenty-six weeks after initiation of sorafenib therapy, CT scanning and RaI imaging studies were repeated. All target lesions were imaged using CT. According to RECIST criteria, bone lesions were not evaluated as target lesions. It was carefully planned that CT scans using i.v. contrast were performed after diagnostic RaI scintigraphies. Procedures to exclude
the occurrence of new bone metastases included bone
and FDG-PET scintigraphy. Patients visited the hospital
every 4 weeks for physical examination and assessment
of laboratory safety parameters. Patients were assessed
for new symptoms, compliance with study medications,
and concomitant medications. Dose adjustments were
made as needed for toxicity. The target serum TSH levels
were below 0.1 mU/l. After completion of 26-week
remission, or stable disease) had been achieved,
treatment, when a favorable response (complete or
progression according to RECIST criteria. Adverse
events were graded with the use of Common Terminol-
ogy Criteria for Adverse Events (version 3).

To study the relation between efficacy and tumor
mutational state, tumor DNA from patients was isolated
from the paraffin-embedded material by taking tissue
punches (diameter, 0.6 mm) with a tissue microarrayer
(Beecher Instruments, Silver Springs, MD, USA) from
tumor and normal areas selected on the basis of a
hematoxylin eosin (HE)-stained slide. Mutational
analysis was performed using PCR amplification
followed by sequencing on an ABI 3730 automated
sequencer (Applied Biosystems, Foster City, CA, USA)
ABI 3700. Codons investigated were: B-type Raf kinase
(BRAF, V600E and exon 11), HRAS (codon 12/13 and
61), KRAS (codon 12/13 and 61), NRAS (codon 61),
and phosphatidylinositol-3-kinase, catalytic, alpha
polypeptide (PIK3CA, exons 9 and 20). Primer
sequences are available on request.

Laboratory parameters

The following laboratory parameters were assessed:
serum TSH, free-thyroxine (T4), thyroglobulin (Tg),
and Tg antibody levels were measured at all visits.
TSH and Tg were also measured 1 and 3 days after
the last rhTSH injection. Safety parameters were
assessed at every visit and included a hematological
profile as well as serum levels of sodium, potassium and
creatinine in lipids, renal and liver function. Serum TSH
was determined with a Modular Analytics E-170 system
(Roche Diagnostic Systems), intra-assay variability:
0.9–10.7%, interassay variability: 0.9–12.1%). Serum
Tg was determined with IRMA (Tg kit, Brahms,
Berlin, Germany) on a Wallac (Wallac, Turku, Finland),
intra-assay variability: 0.1–13.9%, interassay variabil-
ity: 12.3–17.4%). Serum Tg antibodies were determined
with IRMA (Sorin Biomedica, Amsterdam, The Nether-
lands) on a Wallac (Wallac, Turku, Finland, intra-assay
variability: 3.6–4.1%, interassay variability: 11.6%).

Statistical methods

Using a Simon two-stage design, the study required 24
subjects to decide whether the proportion responding,
P, is ≤10% or ≥40%. If the number of responses was
six or more, the hypothesis that P ≤10% is rejected with
a target error rate of 5% and an actual error rate of
2.8%. If the number of responses was five or less, the
hypothesis that P ≥40% is rejected with a target error
rate of 5% and an actual error rate of 4%. All enrolled
patients were included in an intention-to-treat analysis.
Data are reported as mean ± S.D., median (range) or
proportions. Estimates of PFS (time from starting study
drug to progression) with associated 95% CIs were
obtained using the Kaplan–Meier method. Analyses of
variables influencing response to sorafenib were
analyzed with binomial logistic regression (26-week
data). The calculations were performed using SPSS 16.0
for Windows (SPSS, Chicago, IL, USA).

Results

Between 13 October 2007 and 7 October 2008, a total
of 31 patients started sorafenib treatment (Fig. 1).
One patient chose not to start sorafenib therapy after
giving signed informed consent. Therefore, 32 patients
were included in the intention-to-treat analysis. A total
of 22 patients completed 26 weeks of treatment. The
remaining patients discontinued treatment earlier
because of disease progression (four patients, see
efficacy section for details), drug-related adverse events

Figure 1 Study flowchart.
Patients had lung metastases (n BRAFV600E mutations were identified, one of which metastases at multiple sites. In 10/13 patients PTC’s patients had bone metastases. Most patients had Initial TNM stage (no.; %) (5 unknown) thyroid with Hürthle cell metaplasia, the majority of subtype was Hürthle cell carcinoma. In follicular metastases were target lesions this treatment did not aimed at one or more bone metastases. As no bone metastases were target lesions this treatment did not interfere with the assessment of efficacy.

Interestingly, the most common histologic carcinoma subtype was Hürthle cell carcinoma. In follicular thyroid with Hürthle cell metaplasia, the majority of cells were Hürthle cells. At study entry, almost all patients had lung metastases (n=30), whereas 14 patients had bone metastases. Most patients had metastases at multiple sites. In 10/13 patients PTC’s BRAFTV600E mutations were identified, one of which (the tall cell variant) also showed a PIK3CA mutation.

### Table 1 Baseline characteristics.

<table>
<thead>
<tr>
<th>Gender (no.; %)</th>
<th>All patients (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>13 (39)</td>
</tr>
<tr>
<td>Male</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Time from diagnosis (year; median, range)</td>
<td>3 (0–18)</td>
</tr>
<tr>
<td>Age (year; median, range)</td>
<td>65 (53–82)</td>
</tr>
<tr>
<td>Histology (no.; %)</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>13 (41)</td>
</tr>
<tr>
<td>Tall cell</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hürthle cell metaplasia</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Follicular variant papillary</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Follicular</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Hürthle cell metaplasia</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Mixed papillary follicular</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Initial TNM stage (no.; %) (5 unknown)</td>
<td></td>
</tr>
<tr>
<td>T1–3 N0/1 M0</td>
<td>12 (44)</td>
</tr>
<tr>
<td>T4 N0/1 M0</td>
<td>6 (23)</td>
</tr>
<tr>
<td>M1</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Tumor extent at study entry (no.; %)</td>
<td></td>
</tr>
<tr>
<td>Thyroid bed only</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Lungs only</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Lungs and bones only</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Locally advanced* and distant metastases</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Radioiodine dose (GBq, median, range)</td>
<td>15.2 (3.7–30.0)</td>
</tr>
<tr>
<td>External beam radiation (no.; %)</td>
<td>15 (47)</td>
</tr>
</tbody>
</table>

*Including both thyroid bed (n=5) and neck lymph nodes (n=4).

Few additional mutations were identified: one KRAS in FVPTC; two NRAS mutations were found (one in a PTC without a BRAF mutation and one in a FTC); and one additional PIK3CA mutation was found in a FTC with Hürthle cell metaplasia.

### Efficacy

Data on responses are given in Table 2 and Fig. 2. Disease progression led to treatment discontinuation of patients at 6 weeks (one patient with new bone metastases), 18 weeks (one patient with a new abdominal metastasis, one patient with new pulmonary metastases), 25 weeks (one patient with cerebral metastases), 26 weeks (end of 26-week trial: two patients with new bone metastases, one patient with a new pulmonary metastasis), 32 weeks (two patients with new bone metastases, one patient with progression of a hip lesion, one patient with new liver metastases and one patient with new lung lesions) and 40 weeks (one patient with a new neck lesion).

At 26 weeks, 19 patients (59%) had achieved a clinical beneficial response, eight of whom had a partial response (25%) and 11 had stable disease (34%; Table 2). There were no complete responses. At 26 weeks, the cumulative number of patients with progressive disease was seven. Interestingly, four patients with progressive disease based on new lesions had no progression or a considerable decrease in the sum of the longest diameter of target lesions. Radiological response at 26 weeks was not influenced by gender (P=0.593), age (P=0.172), initial tumour lymphnodes metastases (TNM) stage (P=0.488), histology (P=0.614), or the presence of the BRAFTV600E mutation (P=0.760). The prevalence of other mutations was too low to allow statistical analysis. However, when bone metastases were present, the response to sorafenib was significantly worse than in the absence of bone metastases (P=0.004, Table 2).

Although this study was not formally designed for the establishment of PFS, estimation of median PFS was 58 weeks (95% CI, 47–68). Likewise, PFS was influenced by the presence of bone metastases. PFS was 69 weeks (CI: 58–80) in patients without bone metastases and 47 weeks (CI: 32–62) in patients with bone metastases (P=0.046).

In general, Tg response reflected radiological response and there were no differences between the responses of unstimulated versus TSH stimulated Tg measurements (Table 2, Fig. 2). The median time of the nadir of Tg levels was 3 months. The median change in Tg at 26 weeks versus baseline was −16 µg/l (range −2746 to 17 836). Remarkably, one patient with progression in a non-target lesion had a decrease in unstimulated Tg, but an increase in TSH stimulated Tg.

In one 54-year-old woman with pulmonary metastases of a Hürthle cell FTC, a remarkable rise in serum Tg from 1664 to 99 900 µg/l was observed 8 weeks after
initiation of therapy. A chest CT scan revealed an impressive decrease in the number, size, and density of all pulmonary metastases.

Reinduction of radioiodine uptake could be evaluated in 21 patients who had completed 26-week treatment with sorafenib. In one patient, WBS could not be performed for technical reasons. In three patients with extensive metastases, both at baseline and at 26 weeks, RaI WBS revealed uptake at the thyroid bed, but not at the sites of metastases. In 20 patients, there was no RaI uptake at metastatic sites after 26 weeks of sorafenib therapy. In one patient with an occipital skeletal metastasis that did not accumulate RaI at baseline, very slight RaI uptake was observed at 26 weeks. However, a post-therapeutic WBS performed after subsequent 7600 MBq RaI therapy did not reveal any uptake, and consequently it was concluded that no clinically relevant reinduction of RaI therapy had occurred in this patient.

Adverse events
Adverse events led to discontinuation of the study in six patients at respectively 3 weeks (angioedema), 5 weeks (myocardial infarction), 7 weeks (hematuria), 12 weeks (concomitant small cell lung carcinoma), 38 weeks (dyspnea, not related to tumor progression), and 50 weeks (congestive heart disease). Doses were reduced in 18 (56%) patients to control toxicities. The median dose at 26 weeks was 400 mg/day.

The most prevalent adverse events are mentioned in Table 3. The hand–foot syndrome occurred in the first few weeks of treatment and subsided in most patients after dose reduction and topical treatment. Most patients received nutritional support for weight loss. In three patients with considerable weight loss, a percutaneous gastric feeding catheter had to be inserted. Mineral deficiencies were treated with supplementation. Hypertension was treated with antihypertensive drugs. Hematological abnormalities were mild and did not require treatment. In order to maintain serum-free T4 levels and TSH levels at the required values, five patients required a thyroxine dose reduction, whereas in six patients, the dose needed to be increased. No relationship was observed between toxicity and performance state and age.

Discussion
We studied the efficacy of the multiple target tyrosine kinase inhibitor sorafenib in patients with iodine-refractory metastatic DTC, focusing on the reinduction of RaI uptake and the efficacy in patients with bone metastases. After 26 weeks of treatment, we found a partial response rate of 25% and a clinical beneficial response in 59% of the patients. Patients with bone metastases responded significantly worse. Reinduction of RaI uptake as studied by diagnostic WBS was not observed in any patient.
RaI therapy is the only available conventional therapy for patients with metastases of DTC. Hurthle cell carcinomas respond less favorably to RaI, which is compatible with the fact that the most prevalent histology was Hurthle cell metaplasia. The fact that 10/13 PTC harbored BRAFV600E mutations also illustrates the unfavorable prognostic characteristic of our patient group (41). The extensive characterization in recent years of the molecular pathways involved in the pathogenesis of DTC has revealed potential targets for new therapies. The identification of tyrosine kinase activated pathways in DTC together with the advent of novel classes of tyrosine kinase inhibitors has provided new therapeutic perspectives for patients with non-RaI avid DTC. The results of our study with respect to radiological response are comparable with those observed in another study with sorafenib by Gupta et al. (35) and better than observed in the study of Kloos et al. (37). The latter study, however, included patients with anaplastic carcinoma. Comparison of the results of phase II studies with different tyrosine kinase inhibitors in DTC is hampered by differences in patient categories (including histologies, tumor stages, sites of metastases, and tumor extent), study design, and analytical methods. Nonetheless, the results obtained with sorafenib in different studies, including our own, suggest that sorafenib is among the most successful and promising compounds for metastatic DTC. We found a significant difference in the response to sorafenib between patients with or without bone metastases, the latter category responding worse. Nevertheless, 23% of patients with bone metastases had a favorable response. Those patients had metastases at multiple sites, mostly pulmonary that regressed under sorafenib, whereas the bone metastases were stable.

The explanation for a less favorable response of bone metastases is not clear. It can be hypothesized that both pharmacokinetic factors (lower tissue levels in bone) and tumor-related factors are involved. As it is hardly possible to obtain tissue from bone metastases, the relationship between the genetic profile of bone metastases and responsiveness to sorafenib is not easy to study. Another explanation may be that it has been observed that the role of VEGFR signal transduction in tumor propagation in conscript vascular systems such as soft-tissue metastases may differ from less well-defined vascular beds as the bone marrow. As a consequence, VEGFR targeted therapies may have less prominent beneficial effects in bone metastases. In addition it is also conceivable that the presence of bone metastases influences the response of soft-tissue metastases to sorafenib. Although the mechanism is not...
clear it could be hypothesized that the systemic release of proteins or cytokines, such as interleukin 6 or TGF beta from the bone microenvironment plays a role in this phenomenon.

The fact that there was a mixed response in some subjects (both regression and progression) is explained by the heterogeneous nature of metastases in thyroid carcinoma, which can be caused by tumor-related factors and the microenvironment of the metastatic site. This may lead to differences in tumor dependence on tyrosine kinase activated pathways, which may consequently lead to differences in response to sorafenib. RECIST does not take into account these phenomena, which are very important for the selection of lesions that may or may not respond to tyrosine kinase inhibitors.

Another purpose of our study was to assess the effects of sorafenib on RaI uptake. We did not find reinduction of RaI uptake in any patient. Although a clear relation has been found in vitro between genetic alterations in DTC and decreased NIS gene expression (17, 38), multiple mechanisms may be involved in decreased NIS functionality, including impaired NIS membrane trafficking (42, 43), epigenetic changes in NIS and/or NIS promoter genes (44). Although in vitro studies have shown that multiple target tyrosine kinase inhibitors may lead to reinduction of RaI uptake (39, 45), it may well be that these additional mechanisms have prevented a beneficial effect of sorafenib on RaI uptake in our study. Another explanation for the lack of an effect of sorafenib on RaI uptake may be the lower sensitivity of diagnostic WBS as compared to post-therapeutic scintigraphy. For this reason, we used SPECT acquisition in our diagnostic scintigraphies, which has a higher sensitivity than conventional WBS. Nevertheless, we cannot exclude that a limited sensitivity may indeed have contributed to our observation of a failure of sorafenib to reinduce RaI uptake. As baseline CT scans were performed 4 weeks prior to radioiodine scintigraphies, i.e. contrast could have interfered with the diagnostic scintigraphy at baseline. As no urinary iodine measurements were performed, this cannot be entirely ruled out. However, the fact that all patients had negative post-therapeutic WBSSs previously ascertains the true radioiodine non-avid nature of the lesions.

Although uptake of RaI is an important determinant of tumor response, another important factor is radiosensitivity. Indeed, a subgroup of thyroid carcinomas does not respond to RaI therapy, despite RaI uptake. Genetic alterations in radiation-induced apoptotic pathways, including p-53 or cdk-21 may be involved. Therefore, in the design of redifferentiation studies in thyroid carcinoma, this aspect should always be taken into account, ideally involving genetic studies in these pathways.

Serum Tg levels in general paralleled radiological changes. However, tumor lysis during sorafenib or comparable compounds can lead to elevated Tg levels as was observed in one patient. This could be due to tumor lysis, but it could in theory also be caused by increased Tg synthesis as a result of enhanced differentiated behavior of thyroid carcinoma cells.

Although sorafenib therapy had considerable adverse effects, no unexpected or new adverse effects were observed. Most of the adverse effects were temporary and could be managed with dose reduction or therapeutic measures. Weight loss was considerable, especially in patients with low weight at baseline, requiring dietary support or even catheter feeding.

In conclusion, the results of our study confirm the potential role of sorafenib in patients with non-RaI avid metastases of DTC. In addition, we found that patients with bone metastases respond less favorably, and that

### Table 3 Adverse events.

<table>
<thead>
<tr>
<th>Event</th>
<th>All Number of patients (% of total (n=32))</th>
<th>Grades (% of category)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hand foot syndrome</td>
<td>21 (66)</td>
<td>33</td>
</tr>
<tr>
<td>Weight loss</td>
<td>18 (56)</td>
<td>35</td>
</tr>
<tr>
<td>Diarhoea</td>
<td>16 (50)</td>
<td>31</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15 (47)</td>
<td>87</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (47)</td>
<td>60</td>
</tr>
<tr>
<td>Mucositis</td>
<td>14 (44)</td>
<td>100</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (41)</td>
<td>31</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>13 (41)</td>
<td>100</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>9 (28)</td>
<td>100</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>9 (28)</td>
<td>100</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (25)</td>
<td>100</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart disease</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

According to Common Terminology Criteria for Adverse Events (version 3).
diagnostic WBS did not reveal an effect of sorafenib on the reinduction of RaI uptake in these patients. Future phase III studies should confirm the efficacy of sorafenib for DTC.

Declaration of interest
J W Smit received a research grant from Bayer B V Mijdrecht for performing this study. The other authors have nothing to disclose.

Funding
This study was supported by a grant from Bayer B V Mijdrecht, The Netherlands (IMP 12791 19-04-2007).

Acknowledgements
We would like to express our gratitude to Mr Bienvenue Loembe, Bayer B V Mijdrecht, The Netherlands, for the supply of study medication and his technical support and Bayer B V Mijdrecht, The Netherlands, for the supply of study medication and their financial support to this study.

References
2 Mazaferri EL & Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. Journal of Clinical Endocrinology and Metabolism 2001 86 1447–1463.
16 Soares P & Sobrinho-Simoes M. Recent advances in cytometry, cytogenticities and molecular genetics of thyroid tumours and tumour-like lesions. Pathology, Research and Practice 1995 191 304–317.
17 Riesco-Eizaguirre G, Gutierrez-Martinez P, Garcia-Cabezas MA, Nistal M & Santisteban P. The oncogene BRAFV600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na’/I− targeting to the membrane. Endocrine-Related Cancer 2006 13 257–267.

29 Xing M. BRAF mutation in thyroid cancer. Endocrine-Related Cancer 2005 12 245–262.


39 Fenton MS, Marion K, Salem AK, Hogen R, Naeim F & Hershman JM. Induction of cell cycle arrest by sunitinib through inhibition of the MEK/ERK pathway in RET/PTC1 papillary thyroid cancer cells. 90th Annual Meeting of the Endocrine Society. San Francisco (abstract), 1990.


45 Salem AK, Fenton MS, Marion K & Hershman JM. Effect of sunitinib on growth and function of FRTL5 thyroid cells. Thyroid 2008 18 631–635.