Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial

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Summary

Background Patients with radioactive iodine (^{131}I)-refractory locally advanced or metastatic differentiated thyroid cancer have a poor prognosis because of the absence of effective treatment options. In this study, we assessed the efficacy and safety of orally administered sorafenib in the treatment of patients with this type of cancer.

Methods In this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial (DECISION), we investigated sorafenib (400 mg orally twice daily) in patients with radioactive iodine-refractory locally advanced or metastatic differentiated thyroid cancer that had progressed within the past 14 months. Adult patients (≥18 years of age) with this type of cancer were enrolled from 77 centres in 18 countries. To be eligible for inclusion, participants had to have at least one measurable lesion by CT or MRI according to Response Evaluation Criteria In Solid Tumors (RECIST); Eastern Cooperative Oncology Group performance status 0–2; adequate bone marrow, liver, and renal function; and serum thyroid-stimulating hormone concentration lower than 0·5 mIU/L. An interactive voice response system was used to randomly allocate participants in a 1:1 ratio to either sorafenib or matching placebo. Patients, investigators, and the study sponsor were masked to treatment assignment. The primary endpoint was progression-free survival, assessed every 8 weeks by central independent review. Analysis was by intention to treat. Patients in the placebo group could cross over to open-label sorafenib upon disease progression. Archival tumour tissue was examined for BRAF and RAS mutations, and serum thyroglobulin was measured at baseline and at each visit. This study is registered with ClinicalTrials.gov, number NCT00984282, and with the EU Clinical Trials Register, number EudraCT 2009–012007–25.

Findings Patients were randomly allocated on a 1:1 basis to sorafenib or placebo. The intention-to-treat population comprised 417 patients (207 in the sorafenib group and 210 in the placebo group) and the safety population was 416 patients (207 in the sorafenib group and 209 in the placebo group). Median progression-free survival was significantly longer in the sorafenib group (10·8 months) than in the placebo group (5·8 months; hazard ratio [HR] 0·59, 95% CI 0·45–0·76; p<0·0001). Progression-free survival improved in all prespecified clinical and genetic biomarker subgroups, irrespective of mutation status. Adverse events occurred in 204 of 207 (98·6%) patients receiving sorafenib during the double-blind period and in 183 of 209 (87·6%) patients receiving placebo. Most adverse events were grade 1 or 2. The most frequent treatment-emergent adverse events in the sorafenib group were hand–foot skin reaction (76·3%), diarrhoea (68·6%), alopecia (67·1%), and rash or desquamation (50·2%).

Interpretation Sorafenib significantly improved progression-free survival compared with placebo in patients with progressive radioactive iodine-refractory differentiated thyroid cancer. Adverse events were consistent with the known safety profile of sorafenib. These results suggest that sorafenib is a new treatment option for patients with progressive radioactive iodine-refractory differentiated thyroid cancer.

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Introduction

Differentiated thyroid cancer accounts for about 95% of all thyroid carcinomas worldwide. Differentiated thyroid cancer arises from aberrant follicular cells and is classified histologically as either papillary, follicular (including Hürthle cell), or poorly differentiated.[1,2] Generally, the cancer can be treated effectively with surgery, radioactive iodine, and L-thyroxine therapy.[1,2] However, 7–23% of patients develop distant metastases,[3] two-thirds of whom become refractory to radioactive iodine.[4] These patients have a poor prognosis,[4] and the absence of effective therapy (including chemotherapy) makes their clinical management difficult.[5]

Several genetic alterations have been identified in the molecular pathogenesis of thyroid cancer, most frequently RET–PTC translocations and *BRAF*^{V600E} point mutations in papillary thyroid carcinoma, and *RAS* point mutations in follicular and poorly differentiated thyroid carcinoma.[6] *BRAF*^{V600E} has been associated with poor pathological features and poor clinical outcomes in papillary thyroid carcinoma, although not in all studies.[7–10] Increased expression of vascular endothelial growth

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See Online for appendix

factor (VEGF) and its receptors (VEGFR) might have a role in thyroid carcinoma.[11] Anti-angiogenic drugs targeting the VEGF pathway have been assessed in phase 2 studies of radioactive iodine-refractory differentiated thyroid cancer.[12–22] Sorafenib, an oral kinase inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, RET (including RET/PTC), RAF (including *BRAF*^{V600E}), and platelet-derived growth factor receptor β,[23,24] has shown median progression-free survival of longer than 1 year.[12,16–18,20]

We assessed the efficacy and safety of sorafenib versus placebo in patients with progressive, locally advanced, or metastatic radioactive iodine-refractory differentiated thyroid cancer. We did exploratory analyses to identify potential predictive, prognostic, or pharmacodynamic biomarkers.

Methods

Study design and patients

For **full details of the DECISION trial** see http://clinicaltrials.gov/ct2/show/NCT00984282

DECISION was a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial,[25] the study details of which are available online. Participants were enrolled if they met the following key inclusion criteria: age 18 years or older; locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (papillary, follicular [including Hürthle cell], and poorly differentiated) that had progressed within the past 14 months according to Response Evaluation Criteria in Solid Tumors (RECIST); at least one measurable lesion by CT or MRI according to RECIST; Eastern Cooperative Oncology Group performance status 0–2; adequate bone marrow, liver, and renal function; and serum thyroid-stimulating hormone concentration lower than 0·5 mIU/L. Radioactive iodine-refractory differentiated thyroid cancer was defined as the presence of at least one target lesion without iodine uptake; or patients whose tumours had iodine uptake and either progressed after one radioactive iodine treatment within the past 16 months, or progressed after two radioactive iodine treatments within 16 months of each other (with the last such treatment administered more than 16 months ago), or received cumulative radioactive iodine activity of at least 22·3 GBq (≥600 mCi). Patients who had received previous targeted therapy, thalidomide, or chemotherapy for thyroid cancer were excluded; however, low-dose chemotherapy for radiosensitisation was allowed. All patients provided written informed consent. An independent data monitoring committee (comprising three oncologists, an endocrinologist, and a statistician) ensured patient safety and monitored study conduct.

Randomisation and masking

We used an interactive voice response system to randomly allocate patients in a 1:1 ratio to either sorafenib 400 mg (2×200 mg tablets) or matching placebo twice daily (taken 12 h apart without food, at least 1 h before or 2 h after a meal) for a total daily dose of 800 mg. Patients, investigators, and the study sponsor were masked to treatment assignment through the use of unique drug pack numbers that were preprinted onto each bottle or package and assigned to the patient by the interactive voice response system. Randomisation was stratified by age (<60 *vs* ≥60 years) and geographical region (North America *vs* Europe *vs* Asia). Further details of the randomisation procedure are in appendix p 6.

Procedures

Study drug dose interruption or sequential reduction (600 mg [two divided doses: 400 and 200 mg], 400 mg [divided into 2×200 mg doses], and 200 mg daily) and re-escalation were allowed on the basis of specific criteria to manage adverse events (appendix pp 7–11). Treatment continued until progression, unacceptable toxicity, noncompliance, or withdrawal of consent. In the event of protocol-defined progression determined by the investigator, treatment could be unmasked and patients from both groups could begin open-label sorafenib and continue until treatment was no longer beneficial, based on investigator judgment.

Outcomes

The primary endpoint was progression-free survival, assessed every 8 weeks by central independent blinded review with use of modified RECIST criteria (endpoints defined fully in appendix p 12). Secondary endpoints included overall survival, time to progression, objective response rate (complete or partial response), disease control rate (complete response or partial response and stable disease for ≥4 weeks [or ≥6 months in post-hoc analysis]), and duration of response. Progression and objective response were confirmed by a repeat CT or MRI scan at least 4 weeks later. Safety was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Patients were followed up for safety for 30 days after their last study treatment, and then every 3 months for overall survival. Histological diagnoses were assessed retrospectively by an independent pathology panel.

Statistical analysis

With the assumption of a one-sided α of 0·01, 90% power, and a 55·5% increase in median progression-free survival in the sorafenib group compared with placebo, 267 progression-free survival events were needed from 420 enrolled and randomised patients. We assessed progression-free survival, time to progression, and overall survival in all randomised patients by log-rank test with one-sided significance levels of 0·01 (progression-free survival) and 0·025 (time to progression and overall survival). We derived hazard ratios (HRs) and 95% CIs from a Cox proportional hazards model. We assessed objective response rate and disease control rate with the Cochran–Mantel–Haenszel test (one-sided significance level of 0·025) in patients who received the study drug and underwent a baseline

and a post-baseline tumour assessment. All tests were stratified by age (<60 *vs* ≥60 years) and geographical region (North America *vs* Europe *vs* Asia). Summary statistics were provided for safety outcomes during the double-blind period in all randomised patients who received at least one dose of the study drug.

This study is registered with ClinicalTrials.gov, number NCT00984282, and with the EU Clinical Trials Register, number EudraCT 2009–012007–25.

Exploratory biomarker analyses

We also did exploratory biomarker analyses to identify potential predictive, prognostic, or pharmacodynamic biomarker candidates. We gathered archival formalin-fixed, paraffin-embedded biopsies from the primary tumour or metastatic sites from patients who gave consent. With OncoCarta Panel version 1.0 (Sequenom, San Diego, CA, USA) we tested extracted DNA for *BRAF* and *RAS* (including *NRAS*, *HRAS*, and *KRAS*) mutations (listed in appendix p 13). We used IMMULITE 2000 Thyroglobulin (Siemens Diagnostics, Tarrytown, NY, USA) to measure serum thyroglobulin concentrations at baseline and on day 1 of each treatment cycle. We used univariate and multivariate Cox proportional hazards models to study the association between biomarkers and progression-free survival, including a biomarker–treatment interaction term to assess potential differential treatment effects in biomarker-defined subgroups. Multivariate models included *BRAF* and *RAS* mutational status, sex, ethnic origin, age, differentiated thyroid cancer histology, Eastern Cooperative Oncology Group performance status, and treatment group (for models that included both treatment groups).

Role of the funding source

Bayer HealthCare Pharmceuticals and Onyx Pharmaceuticals (an Amgen subsidiary) funded the study design, collection and analysis of data, and interpretation of results. Employees of Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals participated in the study design, data analysis, and interpretation. Data were obtained locally and the central study database was audited by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals. Emma Robinson (7.4 Limited, Oxford, UK) provided medical writing support, which was funded by Bayer HealthCare Pharmaceuticals. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Nov 5, 2009, to Aug 29, 2011, we randomly allocated 419 patients from 77 centres in 18 countries (appendix pp 2–5) to sorafenib (n=209) or placebo (n=210) (figure 1). Two patients in the sorafenib group were randomised twice by mistake; therefore our intention-to-treat population consisted of 417 patients (207 in the sorafenib group and 210 in the placebo group). However, one patient in the placebo group never actually received the study drug, so our safety population comprised 416 patients. Baseline demographic characteristics were well balanced between the treatment groups (table 1). In total, 96·4% (402/417) of patients had distant metastases, most frequently in the lungs (359/417 [86·1%]), lymph

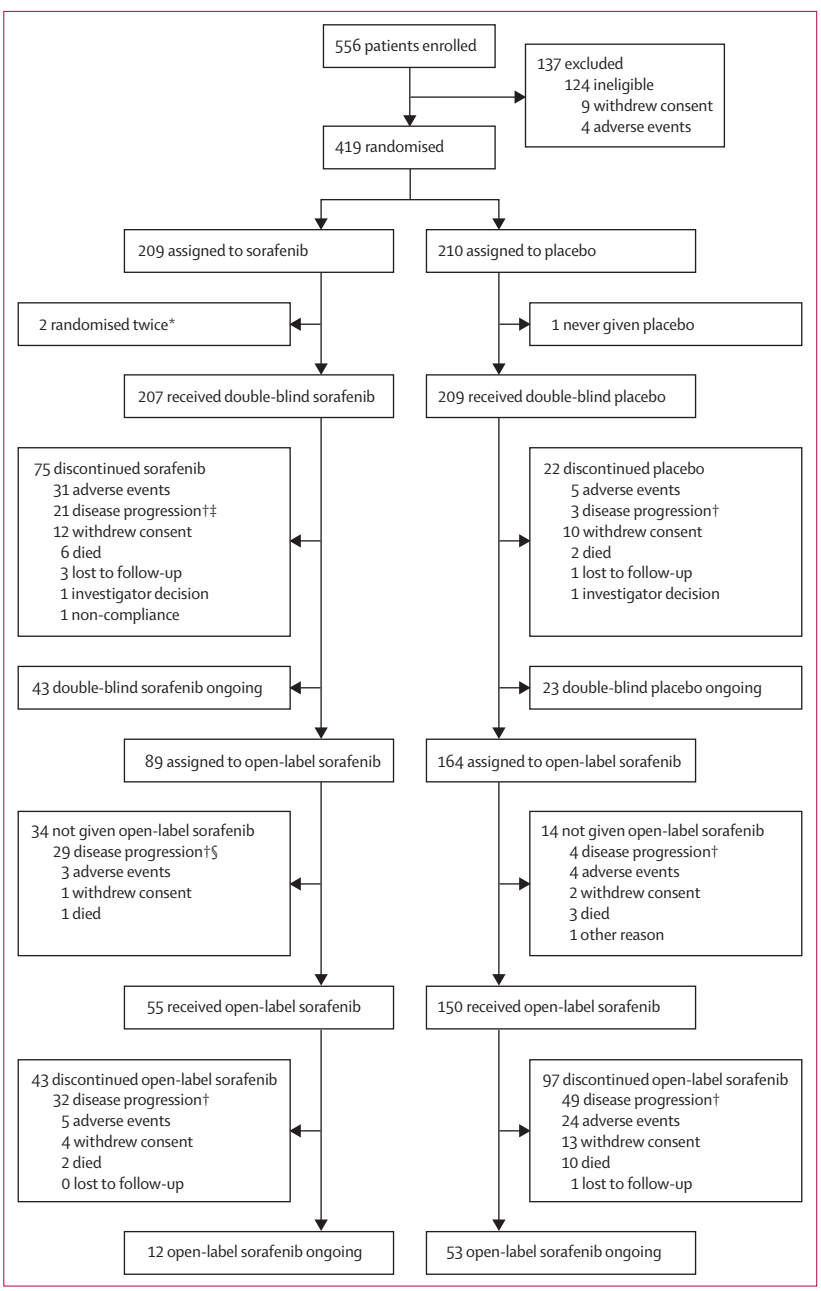

Figure 1: **Trial profile**
ITT=intention-to-treat. *Two patients were randomised twice by mistake and were not included in the ITT population; therefore, the total number of patients in the sorafenib group was 207 and the total ITT population size was 417. †Disease progression, recurrence, or relapse. ‡For one patient receiving double-blind sorafenib, disease progression was by clinical judgment. §For one patient assigned to open-label sorafenib, disease progression was by clinical judgment.

	Sorafenib (n=207)	Placebo (n=210)
Female sex	103 (49·8%)	115 (54·8%)
Age (years)		
Median (range)	63 (24–82)	63 (30–87)
≥60 years	127 (61·4%)	129 (61·4%)
Ethnic origin		
White	123 (59·4%)	128 (61·0%)
Asian	47 (22·7%)	52 (24·8%)
Black	6 (2·9%)	5 (2·4%)
Hispanic	2 (1·0%)	2 (1·0%)
Not reported	29 (14·0%)	23 (11·0%)
Region		
Europe	124 (59·9%)	125 (59·5%)
North America	36 (17·4%)	36 (17·1%)
Asia	47 (22·7%)	49 (23·3%)
Metastases		
Locally advanced	7 (3·4%)	8 (3·8%)
Distant	200 (96·6%)	202 (96·2%)
Time from diagnosis (months)		
Median (range)	66·2 (3·9–362·4)	66·9 (6·6–401·8)
ECOG performance status		
0	130 (62·8%)	129 (61·4%)
1	69 (33·3%)	74 (35·2%)
2	7 (3·4%)	6 (2·9%)
Histology by central review*†		
Papillary	118 (57·0%)	119 (56·7%)
Follicular, oncocytic (Hürthle cell)	37 (17·9%)	37 (17·6%)
Follicular, non-Hürthle cell	13 (6·3%)	19 (9·0%)
Poorly differentiated	24 (11·6%)	16 (7·6%)
Well differentiated	2 (1·0%)	1 (0·5%)
Non-thyroid	0	1 (0·5%)
Medullary	0	1 (0·5%)
Oncocytic carcinoma	2 (1·0%)	0
Carcinoma, not otherwise specified	0	3 (1·4%)
Missing or nondiagnostic	13 (6·3%)	14 (6·7%)
Most common metastatic lesion sites		
Lung	178 (86·0%)	181 (86·2%)
Lymph nodes	113 (54·6%)	101 (48·1%)
Bone	57 (27·5%)	56 (26·7%)
Pleura	40 (19·3%)	24 (11·4%)
Head and neck	33 (15·9%)	34 (16·2%)
Liver	28 (13·5%)	30 (14·3%)
Baseline FDG uptake		
Positive	161 (77·8%)	159 (75·7%)
Negative	14 (6·8%)	15 (7·1%)
Missing	32 (15·5%)	36 (17·1%)
Previous treatment		
Median cumulative radioiodine activity (mCi)	400	376
Any previous systemic anticancer therapy	7 (3·4%)	6 (2·9%)
Any previous radiotherapy	83 (40·1%)	91 (43·3%)

Data are n (%) unless otherwise indicated. FDG=2-(18F)-fluoro-2-deoxy-D-glucose. ECOG=Eastern Cooperative Oncology Group. *All patients had differentiated thyroid cancer according to investigator assessment. †Two patients in the sorafenib group and one in the placebo group were assigned two different histologies on the basis of multiple samples.

Table 1: **Demographic and clinical characteristics of the intention-to-treat population**

nodes (214/417 [51·3%]), and bone (113/417 [27·1%]). More than 75% of patients were positive for fluorodeoxyglucose uptake on PET scintigraphy.

The study met its primary endpoint and showed a significant improvement in median progression-free survival for sorafenib compared with placebo (sorafenib 10·8 months *vs* placebo 5·8 months [HR 0·59, 95% CI 0·45–0·76; p<0·0001]; figure 2A), with a 41% reduction in the risk of progression or death during the double-blind period. Investigator-assessed progression-free survival closely matched that in the central review, with median progression-free survival of 10·8 months in the sorafenib group *vs* 5·4 months in the placebo group (HR 0·49, 95% CI 0·39–0·61; p<0·0001). An exploratory subgroup analysis of progression-free survival showed consistent improvement in all prespecified subgroups (figure 2B). Median time from randomisation until last known follow-up was 16·2 months (range 0·03–33·2 months).

Overall survival did not differ significantly between the treatment groups (HR 0·80, 95% CI 0·54–1·19; p=0·14) (figure 3A). Median overall survival had not been reached at the time of primary analysis data cutoff of Aug 31, 2012. 150 (71·4%) patients receiving placebo crossed over to receive open-label sorafenib at disease progression (figure 1). Furthermore, 42 of 207 (20·3%) patients in the sorafenib group and 18 of 210 (8·6%) patients in the placebo group received subsequent anticancer treatment after the trial. Objective response rate (all partial responses) was 12·2% (24/196) in the sorafenib group, compared with 0·5% (1/201) in the placebo group (p<0·0001). The median duration of response for patients with a partial response to sorafenib was 10·2 months (95% CI 7·4–16·6). More patients experienced tumour shrinkage in the sorafenib group than in the placebo group (figure 3B). For patients without a partial response, stable disease for 4 weeks or longer was recorded in 74% of these patients (294/397 across both groups), and stable disease for 6 months or longer (post-hoc analysis) in 41·8% (82/196) patients in the sorafenib group and 33·2% (67/202) in the placebo group. Disease control rate (partial response plus stable disease for ≥6 months; post-hoc analysis) was 54·1% (106/196) with sorafenib versus 33·8% (68/201) with placebo (p<0·0001). Median time to progression was 11·1 months (95% CI 9·3–14·8) with sorafenib versus 5·7 months (5·3–7·8) with placebo (HR 0·56, 95% CI 0·43–0·72; p<0·0001).

The median duration of treatment was 10·6 months (IQR 5·3–15·7) with sorafenib, and 6·5 months (3·3–12·9) with placebo. The mean daily dose was 651 mg (SD 159) with sorafenib and 793 mg (26) with placebo. Adverse events occurred in 204 of 207 (98·6%) patients receiving sorafenib during the double-blind period and in 183 of 209 (87·6%) patients receiving placebo. These events were mainly grades 1 or 2 (table 2) and tended to occur early in treatment (data not shown). The most frequent adverse events in the sorafenib group were hand–foot skin

reaction, diarrhoea, alopecia, rash or desquamation, fatigue, weight loss, and hypertension (table 2). An increase in serum thyroid-stimulating hormone concentration above 0·5 mIU/L was recorded as an adverse event in 33·3% (69/207) of patients in the sorafenib group, and hypocalcaemia in 18·8% (39/207) (table 2).

Dose interruptions, reductions, or withdrawals because of adverse events occurred in 66·2% (137/207), 64·3% (133/207), and 18·8% (39/207) of patients, respectively, receiving sorafenib, and in 25·8% (54/209), 9·1% (19/209), and 3·8% (8/209) of patients, respectively, receiving placebo. Hand–foot skin reaction was the most common reason for sorafenib dose interruptions (55/207 [26·6%]), reductions (70/207 [33·8%]), and withdrawals (11/207 [5·3%]).

Serious adverse events occurred in 37·2% (77/207) patients receiving sorafenib and in 26·3% (55/209) receiving placebo. Serious adverse events that occurred in 2% or more of patients receiving sorafenib were secondary malignancy (4·3% [9/207]), dyspnoea (3·4% [7/207]), and pleural effusion (2·9% [6/207]); the corresponding rates with placebo were 1·9% (4/209), 2·9% (6/209), and 1·9% (4/209), respectively. In the sorafenib group, secondary malignancies occurred in nine patients, including seven with squamous cell carcinomas of the skin (one patient also had melanoma) and one each with acute myeloid leukaemia and bladder cancer. In the placebo group, there were single cases of bladder cancer, colon carcinoma, pulmonary carcinoid tumours, and gastric cancer. 12 treatment-emergent deaths occurred in the sorafenib group and six in the placebo group. In the sorafenib group, seven deaths were attributable to underlying disease, two to unknown causes, and one each to lung infection, chronic obstructive lung disease, and myocardial infarction. In the placebo group, four deaths were attributable to underlying disease and one each to pulmonary embolism and subdural haematoma. One death in each group was attributed to the study drug—myocardial infarction (sorafenib) and subdural haematoma (placebo).

Tumour mutation data were available for 256 (61·4%) patients overall: 126 in the sorafenib group and 130 in the placebo group. The genetic subpopulation was similar to the overall population, except for a lower percentage of patients from Asia (11·3% [29/256] *vs* 23·7% [99/417]) (appendix p 14). *BRAF* mutations were present in 27·0% (34/126) of tumour samples in the sorafenib group and 33·1% (43/130) of those in the placebo group, and *RAS* mutations in 19·0% (24/126) in the sorafenib group

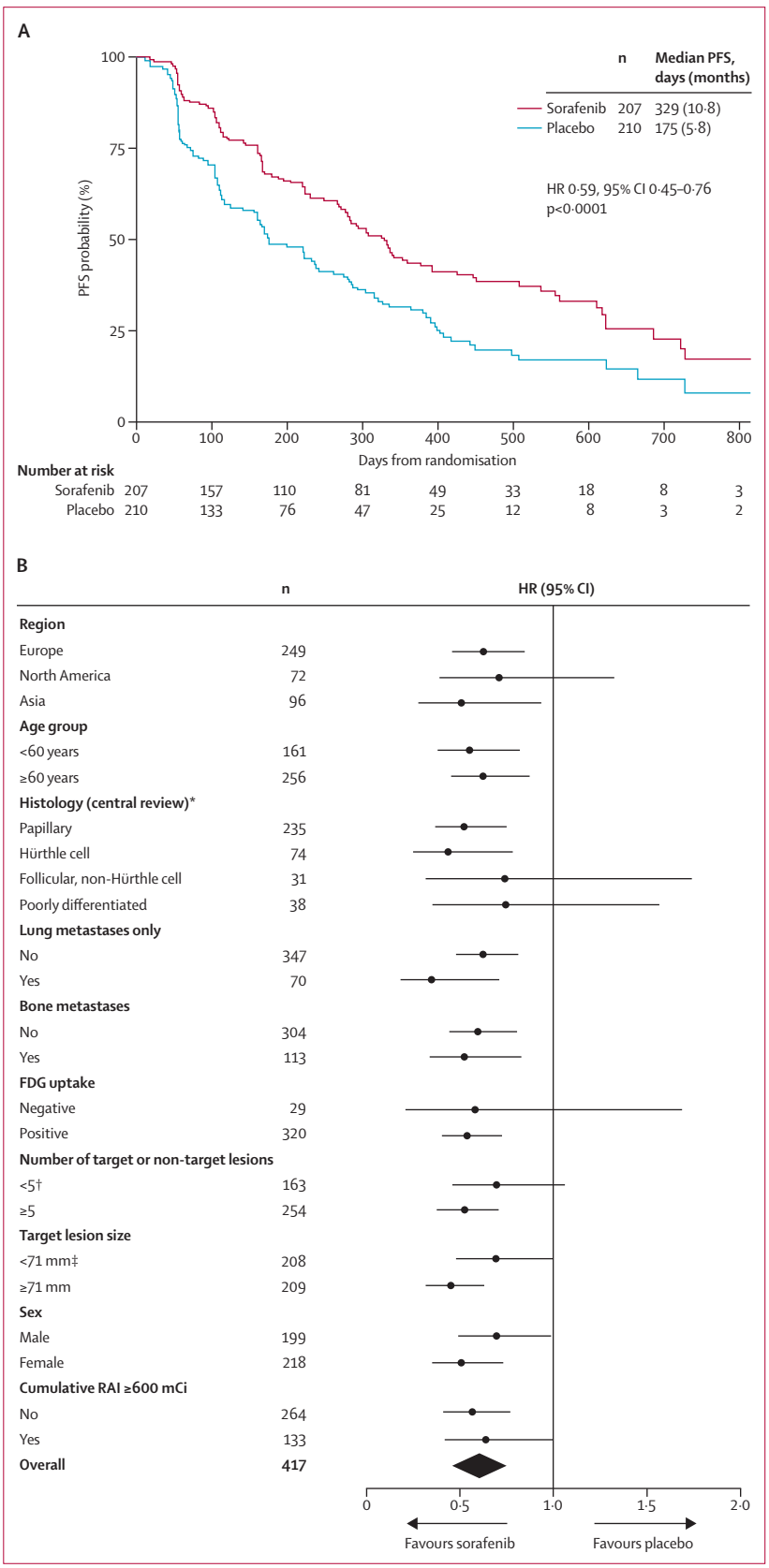

Figure 2: **Progression-free survival**
(A) Progression-free survival by central review (intention-to-treat population). (B) Forest plot of progression-free survival in subgroups (central review). PFS=progression-free survival. HR=hazard ratio. FDG=2-(^{18}F)-fluoro-2-deoxy-D-glucose. RAI=radioactive iodine. *Three patients assigned multiple histologies are excluded. †Five is the median number of lesions. ‡71 mm is the median target lesion size.

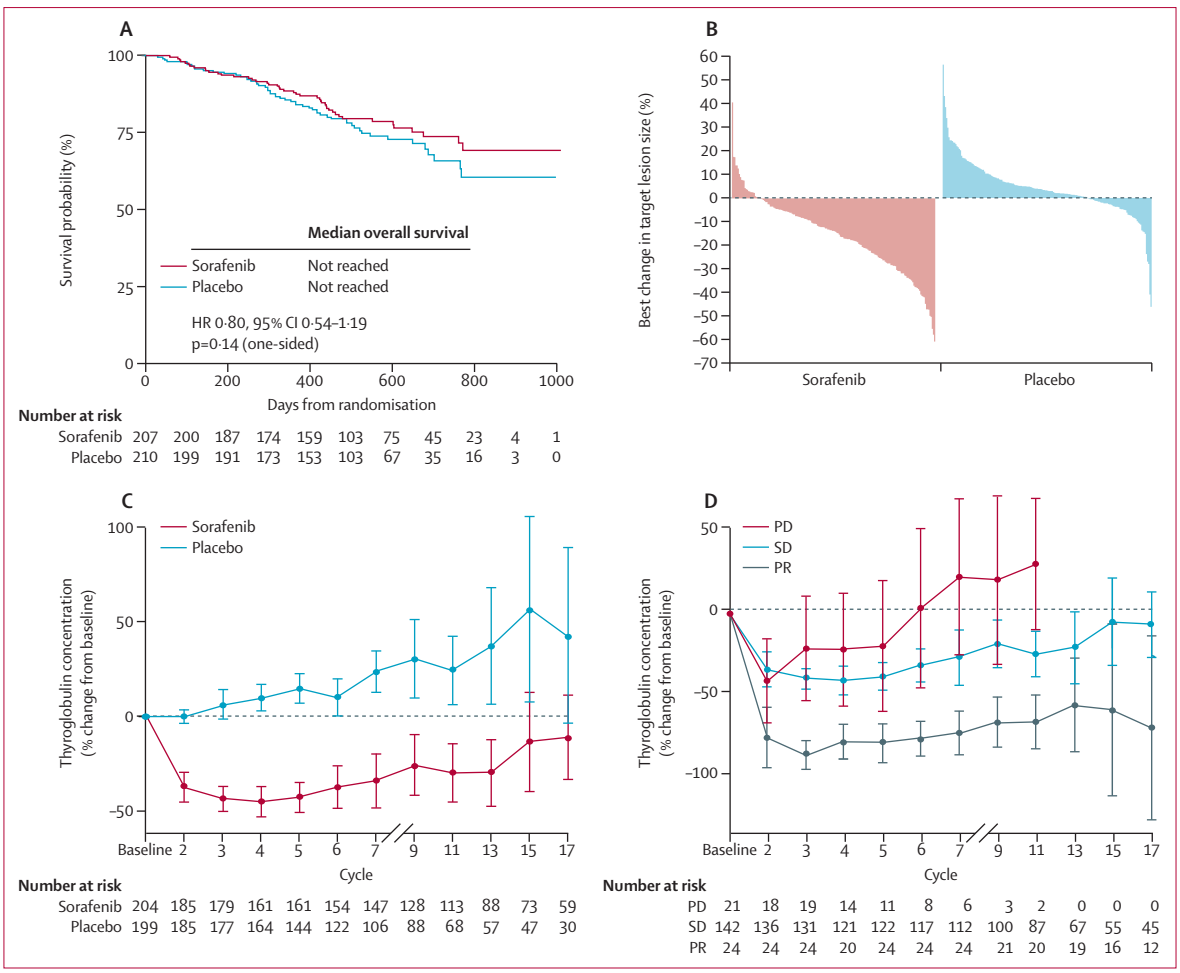

Figure 3: **Overall survival, changes in target lesions, and serum thyroglobulin concentrations**
(A) Kaplan-Meier curve of overall survival. (B) Waterfall plot showing the best change in target lesion size (central review) for individual patients. Best change in target lesion size is defined as the difference in the sum of the longest diameter of the target lesions from baseline. Negative values refer to maximum reduction and positive values to the minimum increase. (C) Changes in thyroglobulin concentrations according to treatment group. (D) Changes in thyroglobulin concentrations in sorafenib-treated patients according to tumour response. Error bars in (C) and (D) are 95% CIs. HR=hazard ratio. PD=progressive disease. SD=stable disease. PR=partial response.

and 20·0% (26/130) in the placebo group. *BRAF* mutation frequency was highest in papillary thyroid carcinoma (46·2% [72/156]), followed by *RAS* mutations (17·9% [28/156]). The frequency of *RAS* mutations was highest in patients with poorly differentiated histology (32·3% [10/31]).

Median progression-free survival was longer in patients with *BRAF* mutations who received sorafenib than in those given placebo (20·5 *vs* 9·4 months; HR 0·46, 95% CI 0·24–0·90; p=0·02; appendix pp 16–17). Sorafenib treatment also doubled median progression-free survival in the wild-type *BRAF* subgroup (8·9 months with sorafenib *vs* 3·8 months without; HR 0·55, 95% CI 0·38–0·79; p<0·001). Similarly, both *RAS* mutation and wild-type subgroups benefited from sorafenib versus placebo; median progression-free survival was 5·5 months with sorafenib versus 3·5 months with placebo in the *RAS* mutation subgroup (HR 0·49, 95% CI 0·24–1·00; p=0·045) and 10·8 months *vs* 5·8 months in the *RAS* wild-type subgroup (HR 0·60, 95% CI 0·42–0·85; p=0·004). Whereas *BRAF* and *RAS* mutations seemed to associate with prognosis, indicated by the difference in median progression-free survival for patients with and without mutations in the placebo group, neither *BRAF* nor *RAS* mutation status was predictive of sorafenib benefit for progression-free survival, evidenced by the similar HRs for sorafenib and placebo in each mutation subgroup (interaction between *BRAF* and progression-free survival treatment effect p=0·653, and interaction between *RAS* and progression-free survival treatment effect p=0·422; appendix pp 16–17). Likewise, multivariate analysis indicated that only histology (papillary *vs* poorly differentiated), age, and sorafenib treatment, but not *BRAF* or *RAS* mutation status, were independently prognostic for progression-free survival benefit (appendix

p 15). Similarly, mutation status was not independently prognostic for progression-free survival when multivariate analysis was restricted to patients with papillary tumours (appendix p 15).

Sorafenib significantly improved median progression-free survival, irrespective of high or low thyroglobulin concentration at baseline (subgroups split according to median values of 449·4 ng/mL; interaction p=0·992 [appendix pp 16–17]). Median serum thyroglobulin concentration increased from baseline throughout treatment in the placebo group, but initially decreased and then paralleled treatment responses in the sorafenib group (figure 3C)—it rose in patients with progressive disease, remained below baseline in patients with stable disease, and decreased further and remained low in patients with partial responses (figure 3D).

Discussion

To our knowledge, our trial is the first phase 3 study in radioactive iodine-refractory differentiated thyroid cancer to be reported (panel). Although this cancer is generally regarded as an indolent disease, patients in the DECISION trial had progressive disease that was refractory to standard treatment with radioactive iodine. Furthermore, a median progression-free survival of 5·8 months and the high incidence of serious adverse events (in a quarter of patients) and dose modifications due to adverse events (in a third of patients) in patients receiving placebo together argue that the inclusion criteria accurately identified a population of patients with radioactive iodine-refractory differentiated thyroid carcinoma with high disease burden and aggressive disease.

	Sorafenib (n=207)			Placebo (n=209)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Hand–foot skin reaction	158 (76·3%)	42 (20·3%)	..	20 (9·6%)	0	..
Diarrhoea	142 (68·6%)	11 (5·3%)	1 (0·5%)	32 (15·3%)	2 (1·0%)	0
Alopecia	139 (67·1%)	..	..	16 (7·7%)	..	..
Rash or desquamation	104 (50·2%)	10 (4·8%)	0	24 (11·5%)	0	0
Fatigue	103 (49·8%)	11 (5·3%)	1 (0·5%)	53 (25·4%)	3 (1·4%)	0
Weight loss	97 (46·9%)	12 (5·8%)	..	29 (13·9%)	2 (1·0%)	..
Hypertension	84 (40·6%)	20 (9·7%)	0	26 (12·4%)	5 (2·4%)	0
Anorexia	66 (31·9%)	5 (2·4%)	0	10 (4·8%)	0	0
Oral mucositis (functional/symptomatic)	48 (23·2%)	1 (0·5%)	1 (0·5%)	7 (3·3%)	0	0
Pruritus	44 (21·3%)	2 (1·0%)	..	22 (10·5%)	0	..
Nausea	43 (20·8%)	0	0	24 (11·5%)	0	0
Headache	37 (17·9%)	0	0	15 (7·2%)	0	0
Cough	32 (15·5%)	0	..	32 (15·3%)	0	..
Constipation	31 (15·0%)	0	0	17 (8·1%)	1 (0·5%)	0
Dyspnoea	30 (14·5%)	10 (4·8%)	0	28 (13·4%)	4 (1·9%)	2 (1·0%)
Neuropathy: sensory	30 (14·5%)	2 (1·0%)	0	13 (6·2%)	0	0
Abdominal pain not otherwise specified	29 (14·0%)	3 (1·4%)	0	8 (3·8%)	1 (0·5%)	0
Pain, extremity (limb)	28 (13·5%)	1 (0·5%)	0	18 (8·6%)	1 (0·5%)	0
Dermatology, other	27 (13·0%)	2 (1·0%)	0	5 (2·4%)	0	0
Voice changes	25 (12·1%)	1 (0·5%)	0	6 (2·9%)	0	0
Fever	23 (11·1%)	2 (1·0%)	1 (0·5%)	10 (4·8%)	0	0
Vomiting	23 (11·1%)	1 (0·5%)	0	12 (5·7%)	0	0
Back pain	22 (10·6%)	2 (1·0%)	0	22 (10·5%)	2 (1·0%)	1 (0·5%)
Pain, other	22 (10·6%)	1 (0·5%)	0	16 (7·7%)	1 (0·5%)	0
Pain, throat, pharynx, or larynx	21 (10·1%)	0	0	8 (3·8%)	0	0
Laboratory						
Metabolic or laboratory— other*	74 (35·7%)	0	0	35 (16·7%)	0	0
Serum TSH increase (MedDRA)*	69 (33·3%)	0	0	28 (13·4%)	0	0
Hypocalcaemia	39 (18·8%)	12 (5·8%)	7 (3·4%)	10 (4·8%)	1 (0·5%)	2 (1·0%)
Increased alanine transaminase	26 (12·6%)	5 (2·4%)	1 (0·5%)	9 (4·3%)	0	0
Increased aspartate aminotransferase	23 (11·1%)	2 (1·0%)	0	5 (2·4%)	0	0

Data are n (%). TSH=thyroid-stimulating hormone. MedDRA=Medical Dictionary for Regulatory Activities. *TSH concentrations higher than 0·5 mIU/L (a study-specific adverse event) are included within this category. Adverse events are reported according to National Cancer Institute–Common Terminology Criteria for Adverse Events version 3.0. Serum TSH increase is reported according to MedDRA version 15.1.

Table 2: **Treatment-emergent adverse events occurring in 10% or more of patients in either group during the double-blind period (safety population)**

The study met its primary endpoint, with a significant and clinically relevant 5-month improvement in median progression-free survival with sorafenib compared with placebo. The progression-free survival benefit was recorded in all prespecified subgroups, including age, sex, geographical region, histology, sites of metastases, and tumour burden. Although the overall response rate was modest in the sorafenib group, target lesions shrank in most patients who were given sorafenib. Similarly, sorafenib increased the disease control rate and prolonged time to progression. Median overall survival was not reached in either group and overall survival did not differ significantly between groups at data cutoff. Overall survival results could be confounded by post-progression crossover from placebo to open-label sorafenib by most patients in the placebo group.

Elucidation of prognostic or predictive biomarkers has potential value in the management of radioactive iodine-refractory differentiated thyroid cancer. *BRAF* and *RAS* mutations have been associated with poor outcomes in patients with differentiated thyroid cancer,[6–10] but less is known about the prognostic or predictive value of these mutations in patients with radioactive iodine-refractory disease. Our exploratory analyses suggest that the patient subset with *BRAF* mutations did better on sorafenib than did those with wild-type *BRAF*, with a median progression-free survival of longer than 20 months. However, this finding seems to be related to the higher predominance of *BRAF* mutations in patients with papillary histology and the overall better outcome of patients with papillary thyroid carcinoma than those with other histologies. Similarly, although patients with *RAS* mutations tended to do worse than those with the wild-type gene, *RAS* mutations were not independently prognostic for progression-free survival. Indeed, sorafenib improved progression-free survival irrespective of *BRAF* or *RAS* mutation status, as evidenced by the similar HRs. Thus, although limited by sample size, these results suggest that *BRAF* and *RAS* mutations are neither independently prognostic nor predictive of sorafenib benefit with regards to prolongation of progression-free survival. Notably, the biomarker analysis subset constituted only 61·4% of the study population (patients who provided genetic consent, from whom tumour samples could be obtained); therefore, these results might be affected by selection bias and imbalances of unknown factors.

The role of monitoring of thyroglobulin in patients with advanced differentiated thyroid cancer during treatment with anti-angiogenic drugs is not well established. In our study, median thyroglobulin concentrations increased gradually in patients given placebo, and initially decreased in patients in the sorafenib group, which suggests that changes might represent disease progression. This theory is underlined by the dynamic changes in median thyroglobulin in patients in the sorafenib group based on their radiological progression. Patients with a partial response had the greatest decrease in median thyroglobulin concentrations, whereas values remained nearer to baseline for patients with stable disease, and initially dropped and then rose in the group of patients with radiological progression. Decreases[13,15,17,21,27] or no change[19] in thyroglobulin concentrations have been reported with anti-angiogenic agents, including sorafenib, in patients with advanced thyroid cancer, but to what extent serum thyroglobulin determination can be used on an individual basis to monitor treatment remains to be established.

Adverse events were generally consistent with the known safety profile of sorafenib. However, some expected side-effects, such as hand–foot skin reaction, alopecia, diarrhoea, hypertension, squamous cell carcinoma of the skin, and hypocalcaemia, were more common than previously reported in renal cell carcinoma and hepatocellular carcinoma phase 3 pivotal trials with sorafenib.[28–30] The reason for the higher frequency of these adverse events is not clear, but could include longer reporting periods for sorafenib or the different dose reduction schema used in this trial to the previous trials (appendix p 7). Hand–foot skin reaction was the most common adverse event in the sorafenib group in DECISION, occurring in 158 of 207 (76·3%) patients, but only 11 of 207 (5·3%) patients discontinued treatment because of this side-effect. Nevertheless, the dermatological adverse events emphasise the importance of monitoring of the skin during sorafenib treatment. The higher incidence of hypocalcaemia was probably related to postsurgical hypoparathyroidism. Increases in thyroid-stimulating hormone above 0·5 mIU/L were reported as an adverse event in a third of sorafenib-treated patients, which suggests that serum thyroid-stimulating hormone levels should be monitored frequently and increases controlled with adjustments in L-thyroxine dose to maintain adequate thyroid-stimulating hormone suppression.

Panel: Research in context

Systematic review

Two previous literature reviews have assessed studies in advanced thyroid cancer[26] and radioactive iodine-refractory differentiated thyroid cancer.[22] We also did a PubMed literature search on Dec 19, 2013, with the terms "clinical trial, phase ii"[Publication Type] AND "thyroid neoplasms"[MeSH terms] (with no restrictions on date or language). This search yielded 50 reports, of which only ten reported phase 2 studies of anti-angiogenic agents in differentiated thyroid cancer. A similar search for phase 3 studies ("clinical trial, phase iii"[Publication Type]) yielded no results in differentiated thyroid cancer, except for the present study design.[25]

Interpretation

Previously, only phase 2 studies of anti-angiogenic agents have been reported in radioactive iodine-refractory differentiated thyroid cancer: axitinib,[15] motesanib,[21] pazopanib,[13] sunitinib,[14] vandetanib,[19] and sorafenib.[12,16–18,20] Therefore, data in this setting are scarce, and the present phase 3 randomised study showing significantly improved progression-free survival with sorafenib versus placebo provides valuable clinical evidence. Our findings suggest that sorafenib represents a new treatment option for patients with progressive radioactive iodine-refractory differentiated thyroid cancer.

The number of deaths in the double-blind part of the study was low in both the sorafenib group and the placebo group, with most causes of death related to underlying disease and only one death in each group attributed to the study drug.

In conclusion, our findings support sorafenib as a new treatment option for patients with radioactive iodine-refractory differentiated thyroid cancer—a setting in which no standard therapy exists at present. Adverse events were generally consistent with the known safety profile of sorafenib. *BRAF* and *RAS* mutations are neither prognostic biomarkers for progression-free survival nor are they predictive biomarkers for radioactive iodine-refractory differentiated thyroid cancer treated with sorafenib. Thyroglobulin concentrations are not predictive for sorafenib benefit, but might be a pharmacodynamic biomarker.

Contributors

All authors participated in writing of the report and approved the final draft. MSB, CMN, BJ, RE, SS, LB, CdlF, FP, RP, YKS, SIS, JWAS, and MJS participated in data collection. MSB, CMN, YKS, SIS, JWAS, JC, CP, IM, CK, and MJS participated in study design, data analysis, and interpretation.

Declaration of interests

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