pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Sorafenib (Nexavar) for Differentiated Thyroid Cancer

July 16, 2015

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effectiveness and safety of sorafenib (Nexavar) in combination with best supportive care (BSC) for the treatment of patients with locally advanced or metastatic, progressive differentiated thyroid cancer (DTC) refractory to radioactive iodine. Sorafenib is a multikinase inhibitor that blocks the receptor tyrosine kinases VEGFR (Vascular Endothelial Growth Factor Receptor) and PDGFR (Platelet Derived Growth Factor Receptor).

The funding request for sorafenib is consistent with the Health Canada indication which is for treatment of patients with locally advanced or metastatic, progressive DTC refractory to radioactive iodine. Sorafenib is available as an oral tablet. The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken twice a day (equivalent to total daily dose of 800 mg).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included international, multicenter, double-blind, placebo-controlled, phase III RCT, DECISION, that evaluated the efficacy and safety of sorafenib compared to placebo in patients (N=419) with locally advanced or metastatic, progressive DTC refractory to radioactive iodine.[1] Baseline characteristics were well balanced across treatment groups. The majority of patients had an ECOG PS score of 0 or 1 (~96%). Even though the study recruited patients with locally advanced disease or distant metastases, the majority of patients had distant metastases (~96%). In addition, there was >70% cross-over from patients in the placebo arm to the sorafenib arm. Final data collection for the primary analysis was carried out in August 2012 and an updated OS analysis was done in May 2013.

Efficacy

The primary outcome of the DECISION trial was progression-free survival (PFS).[1] The median PFS was significantly longer in the sorafenib arm (10.8 months) compared to the placebo arm (5.8 months) (HR 0.59 95%CI 0.45-0.76 p<0.0001).There was a statistically significant longer PFS in favour of the sorafenib arm with a 41% reduction in the risk of progression or death during the double-blind period.

Overall survival and objective response rate (ORR) were secondary outcomes in the DECISION trial. Median overall survival had not been reached at the time of the updated analysis and significant differences in overall survival between the two arms were not reported. Objective response rate was 12.2% vs. 0.5% in the sorafenib and placebo arms respectively with an 11.8% difference between the two arms (95% CI: 7.0% - 16.5%). This was statistically significant difference (p<0.0001) using central assessment.[2]

Two quality of life scales were used in the DECISION trial (EuroQol-5 Dimensions (EQ-5D); Functional Assessment of Cancer Therapy General Version 4.0 (FACT-G)). The QoL scores were lower in the sorafenib arm than in the placebo arm in both scales.[3] The FACT-G scale reported a clinically meaningful decline in QoL. The EQ-5D scale reported statistically significant, but not clinically meaningful decline in QoL for patients in the sorafenib arm compared to patients in the placebo arm.

Harms

Twelve treatment-emergent deaths occurred in the sorafenib group compared to 6 deaths in the placebo group. One death in each group was attributed to the study drug—myocardial infarction (sorafenib) and subdural haematoma (placebo). More patients in the sorafenib arm experienced at least one grade 3 treatment emergent adverse event (TEAE) compared to the patients in the placebo arm (52.7% vs. 23.4%, respectively). For patients receiving sorafenib, about 60% experienced grade 3/4 adverse events or adverse drug reactions.[2] Grade 3 hand and foot syndrome was reported in 20.3% of patients receiving sorafenib, and in no patients receiving placebo. In addition, grade 3 hypertension was reported in 9.7% of patients receiving sorafenib compared to 2.4% of patients receiving placebo. Grade 3 hypocalcaemia also occurred in 5.8% of patients treated with sorafenib and in <1% of patients receiving placebo.

1.2.2 Additional Evidence

pCODR received input on sorafenib from one the following patient advocacy group,Thyroid Cancer Canada. Provincial Advisory Group input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

1.2.3 Interpretation and Guidance

Differentiated thyroid cancer is a malignancy affecting an estimated 4,500 Canadians annually. Surgery and radioiodine therapy is able to manage the disease in the majority of patients. For the 5% and 15% of patients with thyroid cancer who will present with or develop disease which is refractory to radioiodine therapy, there are currently no effective systemic therapy options available. The median survival with radioiodine refractory metastatic thyroid cancer is between 2 ½ and 3 ½ years.[4]

Phase 2 trials showed impressive antitumour activity and an impression of delayed cancer progression in patients with DTC refractory to radioactive iodine. These data led to study of sorafenib in a multicentre randomized double-blind placebo-controlled phase 3 trial (DECISION).[1] In addition to being the first phase 3 trial completed and reported in this population, the trial demonstrated improved progression-free survival (PFS). Objective tumour response rate (ORR) was also improved. However, toxicity was increased compared to placebo, health-related quality of life (HRQoL) was reduced, and overall survival benefit was not proven.

Use of an active control arm in the DECISION trial rather than placebo may have reduced the relative improvements in PFS and ORR compared to placebo, but also would have increased toxicity and perhaps mortality in control patients.

Although the type of adverse effects observed with sorafenib were similar to those seen in other cancers, a higher proportion of DTC patients had more severe grades of toxicity. Grade 4 toxicities were uncommon and only 1 toxic death was observed in the sorafenib arm, and this compares favourably with commonly used cytotoxic agents in the cancer control/palliation setting. An increased number of squamous cell carcinomas of the skin were observed with sorafenib treatment.

Notwithstanding the limitations of the DECISION trial, the unequivocal antitumour effects and lack of treatment options for patients with DTC refractory to radioactive iodine supports the clinical use of sorafenib. The DECISION trial represents a major advance for patients with DTC refractory to

radioactive iodine by demonstrating that phase 3 trials can be successfully conducted for what was considered a rare condition.

There are several caveats to use of sorafenib in these patients. Virtually all of the patients studied had metastatic disease (~96%), so although the benefits for patients with locally advanced disease might be similar, use of local therapies such as palliative surgery and external beam radiation should also be considered for such patients. Although sorafenib is safe, treatment toxicity was increased in these patients who also may have a long natural history of disease. As these patients could be exposed to sorafenib treatment for a lengthy period, this appears to have negative effects on HRQoL, and in the best case scenario treatment is life prolonging but not curative; ideally the decision to initiate treatment with sorafenib should be done by physicians with clinical experience using targeted cancer treatments. Patients should have unequivocal evidence of tumour progression, and the timing of treatment initiation and optimal titration of sorafenib to balance antitumour benefits with adverse effects is essential.

1.3 Conclusions

The Endocrine Clinical Guidance Panel concluded that there is a net overall clinical benefit of sorafenib compared to placebo in patients with clinically progressive radioactive iodine refractory metastatic differentiated thyroid cancer.

One well-conducted randomized placebo controlled phase 3 trial confirms phase 2 evidence and demonstrates improved progression-free survival, tumour objective response rate, and a trend to improved overall survival confounded by crossover.

Toxicity was increased with sorafenib compared both to placebo and to other trials studying sorafenib in cancer, and there may be an increased risk of squamous cell cancers of the skin during sorafenib use. As HRQoL was reduced by sorafenib, the decision to initiate and monitoring of treatment should be done by a clinician experienced in the use of targeted agents and in the treatment of thyroid cancer.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding sorafenib (Nexavar) for differentiated thyroid cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.cadth.ca/pcodr

This Clinical Guidance Report is based on: a systematic review of the literature regarding sorafenib (Nexavar) conducted by the Endocrine Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; and input from the Provincial Advisory Group.

The systematic review is fully reported in Section 6. Background clinical information provided by the CGP, a summary of submitted patient advocacy group Input on sorafenib (Nexavar) and a summary of submitted Provincial Advisory Group (PAG) input on sorafenib (Nexavar) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Sorafenib has a Health Canada indication for treatment of patients with locally advanced or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine.[5] Sorafenib is available as an oral tablet. The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken twice a day (equivalent to total daily dose of 800 mg).

Differentiated thyroid cancer is a malignancy affecting an estimated 4,500 Canadians annually. While surgery and radioiodine therapy is able to manage the disease in the majority of patients, between 5% and 15% of patients with thyroid cancer will present with or develop disease which is refractory to radioiodine therapy. The median survival with radioiodine refractory metastatic thyroid cancer is between 2 ½ and 3 ½ years.[4] For these patients there are currently no effective systemic therapy options available.

2.1.2 Objectives and Scope of pCODR Review

The objective of this review is to evaluate the effectiveness and safety of sorafenib (Nexavar) in combination with best supportive care (BSC) for the treatment of patients with locally advanced or metastatic, progressive differentiated thyroid cancer (DTC) refractory to radioactive iodine.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Study Design and Methods

One double-blind, multicentre randomized controlled trial, DECISION,[1] met the inclusion criteria for the systematic review. The study randomized 419 patients with locally advanced or metastatic radioactive iodine refractory differentiated thyroid cancer to receive sorafenib (n=209) or matching placebo (n=210). Patients received sorafenib or matching placebo. Treatment continued until progression, unacceptable toxicity, noncompliance, or withdrawal of consent. Baseline patient characteristics are listed in

Table 3 and were balanced across arms. The majority of patients had an ECOG Performance Status score of 0 (62.8% vs. 61.4%) or 1 (33.3% vs. 35.2%) in the sorafenib and placebo arms, respectively. The majority of patients also had distant metastasis in the sorafenib and placebo arms (96.6 and % vs. 96.2%, respectively). Patients were stratified at randomization according to age (< 60 vs. ≥ 60 years) and geographic region (North America vs. Europe vs. Asia).

The primary outcome of the DECISION trial was progression-free survival (PFS).[6] Secondary outcomes in the DECISION trial included overall survival (OS), time to progression (TTP), disease control rate (DCR), response rate (RR), duration of response (DoR), and safety including assessment of adverse events and abnormalities in laboratory parameters.[6]

Health Utility Values were measured using the EuroQol-5 Dimensions (EQ-5D). To analyze Health Related Quality of Life (HRQoL), the EQ-5D and the Functional Assessment of Cancer Therapy General Version 4.0 (FACT-G) were used.[2] These results were not reported in the publication of the DECISION study.

All efficacy analyses were carried out in the intent-to-treat population while the safety analyses were conducted in the treated population only (n=416).[1] Final data collection for the primary analysis was carried out in August 2012 and an updated OS analysis was done in May 2013.[7]

Results

The DECISION study met its primary endpoint and showed a statistically significant longer independently assessed PFS in favour of the sorafenib arm with a 41% reduction in the risk of progression or death during the double-blind period. The median PFS was 10.8 vs. 5.8 months in the two arms respectively (HR 0.59 95%CI 0.45-0.76 p<0.0001). Median overall survival had not been reached at the time of the updated analysis and significant differences in overall survival between the two arms were not reported.[1,8]Objective response rate was 12.2% vs. 0.5% in the sorafenib and placebo arms respectively with an 11.8% difference between the two arms (95% CI: 7.0% - 16.5%). This was statistically significant difference (p<0.0001) using central assessment.[2]

FACT-G total scores in the sorafenib arm were lower than in the placebo arm at first assessment (76 ± 15; cycle 2, day 1) and remained steady thereafter. Longitudinal estimates using mixed linear modelling showed that the FACT-G total score was 3.45 points lower in the sorafenib arm compared to the placebo arm, a statistically significant difference (p=0.0006).[3] Based on the accepted minimal clinically important difference (MCID) for FACT-G assessment, this was considered to be a clinically meaningful difference.[2] Statistically significant decreases were also measured in the EQ-5D index and VAS scale for sorafenib compared to placebo (-0.07 and -6.75; p<0.0001, respectively).[3]

Twelve treatment-emergent deaths (occurring up to 30 days from discontinuation of therapy) occurred in the sorafenib group and 6 in the placebo group. One death in each group was attributed to the study drug—myocardial infarction (sorafenib) and subdural haematoma (placebo).[2] More patients in the sorafenib vs. placebo arms experienced at least one grade 3 treatment emergent adverse events (TEAE), 52.7% vs. 23.4% respectively (Table 8). For patients receiving sorafenib, about 60% experienced grade 3/4 adverse events or adverse drug reactions on treatment.[2] Among the adverse events typically associated with the use of tyrosine kinase inhibitors, grade 3 TEAE's were reported in 5.3% vs. 1.4%, 5.3% vs. 1%, 20.3% vs. 0%, 0.5% vs. 0% and 9.7% vs. 2.4% of patients for fatigue, diarrhea, hand and foot syndrome, oral mucositis and hypertension (Table 8). Grade 3 hypocalcaemia also occurred in 5.8% of patients treated with sorafenib. Serious adverse events occurred in 37.2% and 26.3% of patients in the sorafenib and placebo arms, respectively.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplementation questions were identified for this submission.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, patients with radioactive iodine refractory, locally advanced or metastatic differentiated thyroid cancer have extremely limited treatment options. Specifically, TCC noted that for this group, there is an absence of effective treatment options. TCC reported that patients living with this type of thyroid cancer are aware that their advanced disease will progress with worsening symptoms until death, and they embrace opportunities to try new treatment. Therefore, given the stage of disease and time-limited treatment options, respondents reported that they felt that the potential benefit outweighed the possible risks. While there is an expectation that the drug under review may extend survival among patients living with radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer; TCC indicated that the value of extending the time that their cancer is progression-free is also important to patients. TCC reported that by delaying the progression of the disease, the treatment could relieve cancer-related symptoms, and improve or stabilize a patient's quality of life.

PAG Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of sorafenib:

Clinical factors:

- Unmet need for patients with refractory differentiated thyroid cancer

Economic factors:

- Very small patient population

2.2 Interpretation and Guidance

Patients with incurable radioactive iodine refractory differentiated thyroid cancer are currently bereft of reliably effective evidence-based drug treatment options. Historically the rarity of the condition led to a lack of clinical interest in studying conventional agents in randomized trials due to perceived lack of feasibility. As well, existing data from single arm trials and case series has shown limited activity of conventional cytotoxic agents.

The observation of hypothyroidism occurring as an adverse effect of agents inhibiting vascular endothelial growth factor receptor tyrosine kinases (VEGFR TKIs) stimulated interest in studying

these drugs in patients with DTC refractory to radioactive iodine. Phase 2 trials showed impressive antitumour activity and an impression of delayed cancer progression. These data led to study of sorafenib in a multicentre randomized double-blind placebo-controlled phase 3 trial (DECISION). In addition to being the first phase 3 trial completed and reported in this population, the trial demonstrated improved progression-free survival (PFS). Objective tumour response rate (ORR) was also improved. However, toxicity was increased compared to placebo, health-related quality of life (HRQoL) was reduced, and overall survival benefit was not proven.

The DECISION trial was well-conducted and confirms the antitumour effects seen in phase 2 trials, leaving little doubt that the results are genuine. Use of an active control arm rather than placebo may have reduced the relative improvements in PFS and ORR compared to placebo, but also would have increased toxicity and perhaps mortality in control patients. The overall survival benefit of sorafenib was confounded by crossover at the time of progressive disease, although a trend favouring active treatment is apparent. Prolonged overall survival is also apparent in the control arm with the median survival not reached in either arm. Sorafenib was associated with increased toxicity, and HRQoL was reduced although the magnitude of this effect was small on average.

Although the type of adverse effects observed with sorafenib were similar to those seen in other cancers, a higher proportion of patients with DTC refractory to radioactive iodine had more severe grades of toxicity. According to the DECISION trial, 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.[1] Grade 4 toxicities were uncommon and only 1 toxic death was observed in the sorafenib arm, and this compares favourably with commonly used cytotoxic agents in the cancer control/palliation setting. An increased number of squamous cell carcinomas of the skin were observed with sorafenib treatment. Although not observed in other sorafenib cancer trials, this is unlikely coincidence as sorafenib inhibits BRAF, and this has been observed with BRAF inhibiting drugs in cutaneous melanoma.[9,10]

Notwithstanding the limitations of the DECISION trial, the unequivocal antitumour effects and lack of treatment options for patients with DTC refractory to radioactive iodine supports the clinical use of sorafenib. The DECISION trial represents a major advance for patients with DTC refractory to radioactive iodine by demonstrating that phase 3 trials can be successfully conducted for what was considered a rare condition. Although only about 200 DTC patients die annually in Canada,[4] these patients are often not offered any drug treatment due to lack of convincing evidence of benefit.

There are several caveats to use of sorafenib in these patients. Virtually all of the patients studied had metastatic disease (~96%), so although the benefits for patients with locally advanced disease might be similar, use of local therapies such as palliative surgery and external beam radiation should also be considered for such patients. Although sorafenib is safe, treatment toxicity was increased in these patients who also may have a long natural history of disease. As these patients could be exposed to sorafenib treatment for a lengthy period, this appears to have negative effects on HRQoL, and in the best case scenario treatment is life prolonging but not curative; ideally the decision to initiate treatment with sorafenib should be done by physicians with clinical experience using targeted cancer treatments.

Not all patients with radioiodine refractory disease are symptomatic from their cancer. Common symptoms include fatigue, weight loss, pain, need for palliative radiotherapy, and dyspnea. The use of sorafenib in this patient population should be confined to patients who are symptomatic from their cancer or whose cancer is progressing rapidly and who are likely to become symptomatic. Patients should have unequivocal evidence of tumour progression, and the timing of treatment initiation and optimal titration of sorafenib to balance antitumour benefits with adverse effects is essential.

2.3 Conclusions

The Endocrine Clinical Guidance panel concluded that there is a net overall clinical benefit of sorafenib compared to placebo in patients with clinically progressive radioactive iodine refractory metastatic differentiated thyroid cancer.

One well-conducted randomized placebo controlled phase 3 trial confirms phase 2 evidence and demonstrates improved progression-free survival, tumour objective response rate, and a trend to improved overall survival confounded by crossover.

Toxicity was increased with sorafenib compared both to placebo and to other trials studying sorafenib in cancer, and there may be an increased risk of squamous cell cancers of the skin. As HRQoL was reduced by sorafenib, the decision to initiate and monitoring of treatment should be done by a clinician experienced in the use of targeted agents and in the treatment of thyroid cancer.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Endocrine Clinical Guidance Panel. It is not based on a systematic review of the literature.

3.1 Description of the Condition

Differentiated thyroid cancer is a malignancy affecting an estimated 4,500 Canadians annually. For most of these patients their disease is manageable with surgery and radioiodine therapy. About 85% of patients diagnosed with thyroid cancer have excellent outcomes with a high rate of cure and potential for long term survival.

Unfortunately, a small percentage of patients (about 15%) will progress to metastatic disease and for many of these patients radioiodine therapy is an effective way of managing their metastatic cancer.

Between 5% and 15% of patients with thyroid cancer will present with or develop disease which is refractory to radioiodine therapy. These patients have no effective systemic therapy options available to them at the present time in Canada.

The median overall survival for patients with radioactive iodine refractory differentiated thyroid cancer is between 2 ½ and 3 ½ years. Last year in Canada there were approximately 200 deaths from metastatic thyroid cancer.[4]

DTC refractory to radioactive iodine is a rare condition. For those affected by this, there is a significant risk of death from their disease and at present there are no good systemic therapy options.

3.2 Accepted Clinical Practice

Palliative treatment with doxorubicin (Adriamycin) has been regarded as an accepted standard of care based on medical literature from the 1980s that suggested response rates of 20%. More recent literature from clinical trials shows that the response rates to doxorubicin are substantially lower than that, around 5%.[11] The endocrinologists and medical oncologists who treat this condition rarely offer such treatment to patients because of the poor efficacy and significant toxicity. Patients with DTC refractory to radioactive iodine are left with the options of repeated surgery to manage recurrent disease in the neck, and external beam radiation therapy to deal with symptoms from metastatic bone and lung disease such as pain and hemolysis. The tyrosine kinase inhibitors have demonstrated activity in DTC refractory to radioactive iodine based on numerous phase II studies with agents including sorafenib, sunitinib, and others.

Numerous sets of guidelines including the National Comprehensive Cancer Network (NCCN), the American Thyroid Association (ATA), the European Thyroid Association (ETA), the European Society for Medical Oncology (ESMO), and the Latin American Thyroid Society (LATS) all include recommendations for enrollment in clinical trials for this patient population or the use of tyrosine kinase inhibitors.

3.3 Evidence-Based Considerations for a Funding Population

The expected patient population in Canada for whom treatment with sorafenib would be considered is small. There were just over 180 deaths from metastatic thyroid cancer in

Canada in 2013. Of 4,500 patients diagnosed with thyroid cancer across Canada in a year as much as 15% of that patient population will develop radioiodine refractory disease over the course of their illness. Not all patients with radioiodine refractory disease would be appropriate candidates for treatment with tyrosine kinase inhibitors such as sorafenib, due to various reasons including advanced disease or poor performance status (ECOG $\geq$3).

This treatment would be limited to patients with demonstrable metastatic disease who are radioiodine refractory according to accepted definitions of radioiodine refractory disease. Not all patients with radioiodine refractory disease are symptomatic from their cancer. Common symptoms include fatigue, weight loss, pain, need for palliative radiotherapy, and dyspnea. The use of sorafenib in this patient population would be confined to patients who are symptomatic from their cancer or whose cancer is progressing rapidly and who are likely to become symptomatic.

3.4 Other Patient Populations in Whom the Drug May Be Used

Patients with metastatic thyroid cancer are managed primarily with thyroid stimulating hormone (TSH) suppression using super physiologic doses of thyroid replacement. Their TSH and thyroglobulin levels are assessed on an ongoing basis to ensure TSH suppression is maintained and to monitor disease progression biochemically. Patients with biochemical evidence of progression alone (increasing thyroglobulin) would not be considered for treatment with sorafenib unless they develop evidence of overt metastatic disease.

In the setting of the treatment of thyroid cancer there are rare patients who present with primary tumours within the thyroid gland that are not amendable to surgical resection or where surgical resection requires distinguishing treatment to the neck that can necessitate a laryngectomy. Patients are sometimes unwilling to consider such treatment recognizing the morbidity associated with it. Therapeutic options for this patient population are limited, as radioiodine therapy cannot be administered in the setting of an intact thyroid gland.

Patients who are not candidates for surgery or who refuse the disfiguring surgery that may be required are candidates for external beam radiation therapy to their thyroid gland but otherwise therapeutic options are extremely limited for these patients. The inability to safely give radioiodine therapy eliminates the most effective treatment option from the treating physician's armamentarium. This is a patient population in whom there may be a role for treatment with sorafenib but where there is presently limited evidence supporting its use.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Thyroid Cancer Canada (TCC), provided input on sorafenib (Nexavar) for the treatment of patients with locally advanced or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine, and their input is summarized below.

TCC obtained the information using a number of approaches. TCC conducted phone interviews with two (2) patients who had direct experience with sorafenib. TCC also conducted a literature review of printed sources reports to identify issues and experiences that are commonly shared among many people living with thyroid cancer.

From a patient perspective, patients with radioactive iodine refractory, locally advanced or metastatic differentiated thyroid cancer have extremely limited treatment options. Specifically, TCC noted that for this group, there is an absence of effective treatment options. TCC reported that patients living with this type of thyroid cancer are aware that their advanced disease will progress with worsening symptoms until death, and they embrace opportunities to try new treatment. Therefore, given the stage of disease and time-limited treatment options, respondents reported that they felt that the potential benefit outweighed the possible risks. While there is an expectation that the drug under review may extend survival among patients living with radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer; TCC indicated that the value of extending the time that their cancer is progression-free is also important to patients. TCC reported that by delaying the progression of the disease, the treatment could relieve cancer-related symptoms, and improve or stabilize a patient's quality of life.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission and have not been corrected.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients Have with DTC

Because of the nature of thyroid cancer, TCC indicated that patients may or may not experience symptoms related to their cancer that have a negative impact on their quality of life or daily routines.

TCC noted that the cancer can create growths that are visible, which can affect swallowing and eating. As the cancer progresses and develops metastases in other areas of the body, patients can experience symptoms related to the decreased effectiveness of other organs, for example, difficulty breathing when it is present in the lungs.

TCC reported that for some patients, there are very few symptoms; however, the cancer continues to progress silently, and for this group of patients, will result in death. Patients will be looking at making decisions concerning palliative and end-of-life care, and making arrangements with their families.

4.1.2 Patients' Experiences with Current Therapy for DTC

According to TCC, patients with radioactive iodine refractory, locally advanced or metastatic differentiated thyroid cancer have extremely limited treatment options. TCC noted that for this group, there is an absence of effective treatment options.

TCC indicated that the goals of current treatment options for radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer include: (1) controlling the progression of the disease (extending life), and (2) reducing cancer-related symptoms (extending or stabilising quality of life).

4.1.3 Impact of DTC and Current Therapy on Caregivers

Although caregivers provide loving support, TCC reported that caregivers who are responsible for palliative and end-of-life care experience a high level of stress and anxiety, as well as exhaustion and burnout. Moreover, caregivers are also experiencing emotional stress as they are preparing for the end of life of their loved ones.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Sorafenib

According to TCC, there is an expectation that this drug would extend survival among patients living with radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer.

> TCC further noted that the value to patients of extending the time that their cancer is progression-free cannot be overestimated. Patients living with this type of thyroid cancer are aware that their advanced disease will progress with worsening symptoms until death, and they embrace opportunities to try new treatment.

TCC reported that by delaying the progression of the disease, this treatment could relieve cancer-related symptoms, and improve or stabilise a patient's quality of life. The most common side effects reported by patients in the clinical trial were hand-foot skin reaction, diarrhea, alopecia, and rash.

> As such, TCC believes that when living with no or with minimal cancer-related symptoms, and with minimal side effects from the treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

Based on the information gathered from the two respondents who had experienced with sorafenib, both respondents indicated that the drug was responsible for slowing down the progression of the disease, and is responsible for extending their life. One respondent reported experiencing success with sorafenib for just over two months before it was no longer effective, while the second respondent indicated that they had experienced success for three years before it was no longer effective.

> Both respondents indicated that their quality of life while taking this treatment was good, despite some negative side effects.

After having completed treatment with sorafenib, both respondents believed that the benefits of the treatment have outweighed any risks and adverse side-effects. One respondent stated: *"I had fewer side effects than I anticipated. I was scared to take it. I thought I wouldn't be able to move off the couch. And I was like "wow, this is kind of nice".*

Neither respondents were able to identify an adverse effect or symptom that had a serious negative impact on their personal quality of life, or on the quality of life of their caregivers. The following symptoms below were identified by one or both respondents. It is important to note that respondents reported that these symptoms were manageable for as long as the treatment remained effective for them.

- Diarrhea
- Tingling in the fingers
- Muscle and joint pain
- Bruising and bleeding easily
- Mild headaches
- Nausea, low appetite

According to TCC, the most impactful side effect was diarrhea for both respondents. The respondents reported the following:

"I'd be driving and I'd have to stop and find a tree. I was taking Immodium, but when I took that, then I couldn't go, and that was too painful. I'd rather run to the bathroom and go instead because constipation is no fun."

"The diarrhea kept getting worse, and I was taking the maximum dose of Immodium. At the end it meant I couldn't leave the house because I couldn't go too far from the bathroom. I wouldn't go out to social events".

One respondent noted that the nausea and headaches made concentrating and travelling in the car unpleasant. "*I didn't feel like doing much. I just wanted to lie around and watch tv. I'd try to go on the computer and try to research things, and just had a short attention span."*

Both respondents expressed that despite experiencing side effects such as diarrhea, nausea and headaches that restricted what they were able to do on a day-to-day basis, they had a good quality of life, and indicated that the therapy had no serious negative impact on the following activities:

- Spending time with loved ones, including playing with grandchildren
- Maintaining friendships
- Self-managing other health concerns

Both respondents also expressed concern over the costs of the treatment, indicating that new treatments often come with high costs which must be covered by patients out of pocket, or which require lengthy processes for public and private insurance to secure approval for the expense.

In summary, both respondents stated that they felt very lucky to have been given the opportunity to participate in the clinical trial for the drug, and felt that the benefits of the medication greatly outweighed any negative impact of the side effects.

"It meant everything. I felt privileged to be a part of it. I am open to anything to try to get rid of the cancer"

"Access means a lot. If I didn't have that…well, I didn't have any other options"

4.3 Additional Information

N/A

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group (PAG) includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of sorafenib:

Clinical factors:

- Unmet need for patients with refractory differentiated thyroid cancer

Economic factors:

- Very small patient population

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that there is no current standard of care for the treatment of differentiated thyroid cancer that is refractory to radioactive iodine. Some patients may be treated with doxorubicin based therapy and other patients would receive best supportive care.

5.2 Factors Related to Patient Population

There is a small number of patients with radioactive iodine refractory differentiated thyroid cancer. There is an unmet need for these patients and sorafenib will provide a treatment option for these patients.

5.3 Factors Related to Dosing

The dose of sorafenib for treatment of differentiated thyroid cancer is 400mg (two 200mg tablets) taken orally twice daily, which is the same dose as for other cancers. Sorafenib, being available in only one strength, is easier for patients to manage dosage adjustments and there would be no wastage due to dosage adjustments which are managed by increasing the dosing interval rather than changing the dose. These are enablers to implementation.

5.4 Factors Related to Implementation Costs

PAG noted there would be a small incremental budget impact due to the small number of patients who would not have previously received treatment.

5.5 Factors Related to Health System

PAG noted that sorafenib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.6 Factors Related to Manufacturer

None identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of sorafenib (Nexavar) in combination with best supportive care (BSC) for the treatment of patients with locally advanced or metastatic, progressive differentiated thyroid cancer (DTC) refractory to radioactive iodine.

No relevant supplemental questions were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

[Table 1]. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized controlled trials	Adult patients with locally advanced or metastatic progressive differentiated thyroid cancer who are refractory to radioactive iodine. Subgroups: • Locally advanced • Metastatic disease • By histological subtype (papillary, follicular and Hürthle), poorly differentiated • Age • Symptomatic vs. asymptomatic DTC	Sorafenib (Nexavar) (400mg orally, twice daily) + BSC	BSC (Bisphosphonate, denosumab) Doxorubicin Other TKI's (sunitinib, axitinib, pazopanib or vandetanib, lenvatinib**) Surgical resection External beam radiation therapy (EBRT) Clinical trials	**OS** **PFS** **QoL** AE's • Hand and foot syndrome • Mucocytosis • Diarrhea • Hypertension • fatigue SAE's WDAE

OS: overall survival; PFS: progression free survival; QoL: quality of life; AE: adverse events; SAE: serious adverse events; WDAE: withdrawal due to adverse events; ECOG PS: eastern co-operative oncology group performance status; TKI: tyrosine kinase inhibitor; BSC: best supportive care

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

***Identified as agent of interest although not currently available in Canada*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were sorafenib or Nexavar or Bay-43-9006 or BAY-5459085 or HSDB-5739.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of April 1, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

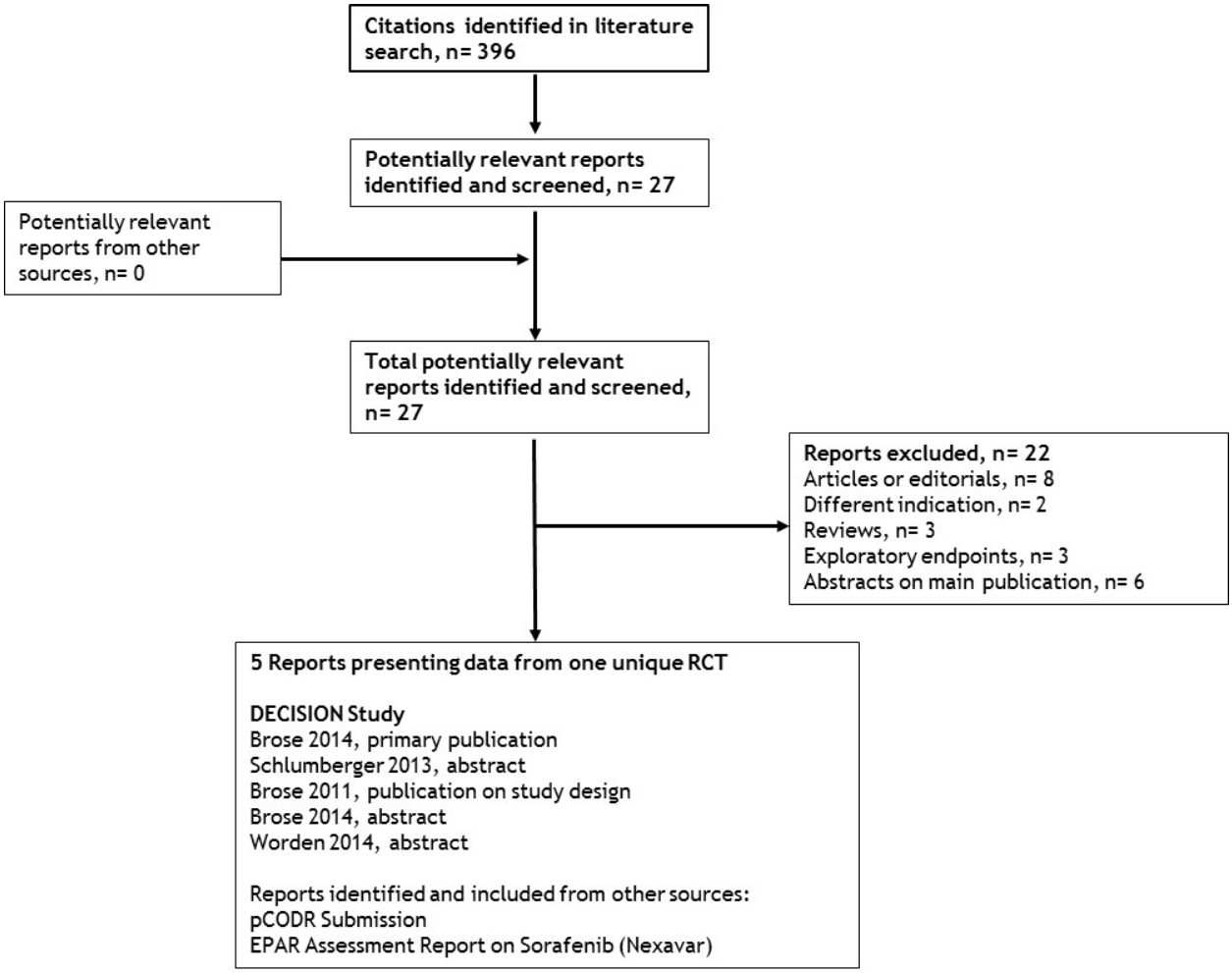
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 27 potentially relevant reports identified, 5 reports presenting results from one RCT were included in the pCODR systematic review and 16 studies were excluded. Studies were excluded because they were articles or editorials,[12-19] provided data on a different indication or line of therapy,[15,20] were reviews,[21-23] presented results that were part of the primary publication,[24-29] or presented results for exploratory endpoints,[30-32] from the DECISION trial which were not specified as part of the pCODR review protocol.

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the DECISION study was also obtained through requests to the Submitter by pCODR[33]

6.3.2 Summary of Included Studies

One double blind phase 3 randomised controlled trial, DECISION,[1] was included in the systematic review.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of trial characteristics of the included study, DECISION[1] for patients with locally advanced or metastatic radioactive iodine refractory differentiated thyroid cancer who are refractory to radioactive iodine.

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT00984282 Funded by: Bayer Double blind phase 3 RCT, randomized in a 1:1 ratio (sorafenib : placebo) Randomized: n= 419 Final analysis - August, 2012 Updated analysis- May 31, 2013[8]	Adults (≥18 years of age) ECOG PS 0-2 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 RECIST At least one measurable lesion by CT or MRI according to RECIST Adequate bone marrow, liver, and renal function; and serum thyroid-stimulating hormone concentration lower than 0.5 mIU/L <u>Exclusion criteria:</u> Histologic subtypes of thyroid cancer other than differentiated (i.e. like anaplastic and medullary carcinoma, lymphoma or sarcoma) Prior anti-cancer treatment with tyrosine kinase inhibitors, monoclonal antibodies (licensed or investigational) that target VEGF (vascular endothelial growth factor) or VEGF Receptors or other targeted agents Prior anti-cancer treatment for thyroid cancer with use of chemotherapy (low dose chemotherapy for radiosensitization is allowed) or Thalidomide or any of its derivatives	**Intervention:** Sorafenib **Comparator:** Placebo	**Primary:** PFS (independent blinded review committee) **Secondary:** OS Time to progression ORR Disease control rate Duration of response Safety: • Treatment emergent adverse events • Dose reductions interruptions and treatment discontinuation **Exploratory analysis:** HRQoL The primary efficacy analysis was carried out in the intent-to-treat population. The OS and TTP analyses were carried out in the intent-to-treat population whereas the RR, DCR and DOR analyses were carried out in the per protocol population.

Table 2. Summary of trial characteristics of the included study, DECISION[1] for patients with locally advanced or metastatic radioactive iodine refractory differentiated thyroid cancer who are refractory to radioactive iodine.			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
RECIST= Response Evaluation Criteria in Solid Tumours; RCT= randomized controlled trial; PS= performance status; PFS: progression free survival; ORR: objective response rate; OS: overall survival; HRQoL: health related quality of life			

a) Trials[1]

One double blind randomized controlled trial, DECISION,[1] met the inclusion criteria for the systematic review. Baseline patient characteristics are listed in Table 3. Enrollment was from Nov 5, 2009, to Aug 29, 2011 from 91 sites in 18 countries within North America, Europe and Asia.[6] Patients with locally advanced or metastatic radioactive iodine refractory differentiated thyroid cancer were included in the study. 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 were stratified at randomization according to age (< 60 vs. ≥ 60 years) and geographic region (North America vs. Europe vs. Asia). The method of randomization was generated by an interactive voice response system to randomly allocate patients in a 1:1 ratio to either sorafenib or placebo. Unique drug pack numbers preprinted onto each bottle or package and assigned to the patient by the interactive voice response system were used to mask patients, investigator, and the study sponsor to treatment assignment. Two hundred and sixty seven progression-free survival events were needed from 420 enrolled and randomized patients to have 90% power to detect a 55.5% increase in mPFS in the sorafenib group compared with placebo with the assumption of a one-sided α of 0.01.

The primary outcome of the DECISION trial was PFS. The study authors noted that because PFS may better predict improvement in overall survival (OS) than response rate, PFS was selected as the primary efficacy assessment.[6] Secondary objectives in the DECISION trial included OS, measured from date of randomization to date of death due to any cause; time to progression (TTP), measured from date of randomization to date of confirmed radiologic progression; disease control rate (DCR); response rate (RR); duration of response (DoR); and safety including assessment of AEs and abnormalities in laboratory parameters.[6]

Health Utility Values were measured using the EuroQol-5 Dimensions (EQ-5D). To analyze Health Related Quality of Life (HRQoL), the EQ-5D and the Functional Assessment of Cancer Therapy General Version 4.0 (FACT-G) were used.[2] Questionnaires were self-administered at baseline and day 1 every 28-day cycle.[3] Higher scores represented better health status for the EQ-5D. On the EQ-5D index, a change of at least 0.10 to 0.12 points was considered clinically meaningful (using ECOG PS as the anchor). A change of at least 7 points on the VAS was considered as clinically meaningful for the EQ-5D VAS questionnaire. The total score of the FACT-G ranged from 0 to 108; the higher the score, the better the QoL. Important Difference of 3 to 7 points was considered to be important for the FACT-G total score.[2]

The primary efficacy analysis was carried out in the intent-to-treat population. The secondary efficacy analyses, OS and TTP, were carried out in the intent-to-treat population whereas the RR, DCR and DOR analyses were carried out in the per protocol population. The safety analyses

were conducted in the treated population only (n=416).[1] Final data collection for the primary analysis was carried out in August, 2012 and an updated OS analysis was done in May 31, 2013.[7] Patients were followed up for safety for 30 days after their last study treatment, and every 3 months for overall survival.

Bayer HealthCare Pharmceuticals and Onyx Pharmaceuticals (an Amgen subsidiary) funded and participated in the study design, collection and analysis of data, and interpretation of results.[1]

b) Populations[1]

Baseline patient characteristics were balanced across arms (Table 3). The median age of patients was 63 and 63 years in the sorafenib vs. placebo arms, respectively with 61.4% of patients in both arms being 60 years or older. The majority of patients also had an ECOG PS score of 0 (62.8% vs. 61.4%) or 1 (33.3% vs. 35.2%) in the sorafenib vs. placebo arms, respectively. The majority of patients also had distant metastasis in the sorafenib and placebo arms (96.6% and 96.2%, respectively). The submitter confirmed through the Checkpoint meeting that no Canadian patients were enrolled in the study.

Table 3. Baseline Patient Characteristics of all randomized patients in the DECISION trial[1]

Characteristic	Sorafenib, n=207	Placebo, n=210
Age (years), n (%)		
Median	63	63
Range	24-82	30-87
Age Distribution, n (%)		
≥60 years	127 (61.4)	129(61.4)
Sex, n (%)		
Female	103 (49.8)	115 (54.8)
Race, n (%)		
White	123 (59.4)	128 (61.0)
Hispanic	2 (1.0)	2 (1.0)
Black	6 (2.9)	5 (2.4)
Asian	47 (22.7)	52 (24.8)
Not Reported	29 (14.0)	23 (11.0)
Region, n (%)		
Europe	124 (59.9)	125 (59.5)
North America	36 (17.4)	36 (17.1)
Asia	47 (22.7)	49 (23.3)
ECOG PS, n (%)		
0	130 (62.8)	129 (61.4)
1	69 (33.3)	74 (35.2)
2	7 (3.4)	6 (2.9)
Site of metastatic disease, n (%)		
locally advanced	7 (3.4)	8 (3.8)
Distant	200 (96.6)	202 (96.2)
Histology by central review, n (%)*†		
Papillary	118 (57.0)	119 (56.7)
Follicular, oncocytic (Hürthle cell)	37 (17.9)	37 (17.6)
Follicular, oncocytic (non-Hürthle cell)	13 (6.3)	19 (9.0)
Poorly differentiated	24 (11.6)	16 (7.6)

Table 3. Baseline Patient Characteristics of all randomized patients in the DECISION trial[1]		
Characteristic	**Sorafenib, n=207**	**Placebo, n=210**
Missing or nondiagnosed	13 (6.3)	14 (6.7)
Notes: PS= performance status; *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.		

c) Interventions

DECISION randomized 419 patients in a 1:1 ratio to receive sorafenib (n=209) or matching placebo (n=210). Patients received 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. Treatment continued until progression, unacceptable toxicity, noncompliance, or withdrawal of consent. Dose interruption or sequential reduction and re-escalation were allowed on the basis of specific criteria to manage adverse events. Dose reductions were in 200mg increments starting at 600 mg [two divided doses: 400 and 200 mg], 400 mg [divided into 2 × 200 mg doses], and 200 mg daily). Re-escalation of therapy was allowed.

The median duration of therapy was 46 (range 0.3-135) vs. 28 (range 1.7-132) weeks in the sorafenib vs. placebo arms. Median daily dose in the sorafenib arm was 708.4mg/day.[2]

d) Patient Disposition

The disposition of the patients at the time of the primary analysis for progression-free survival (data cut off: August 2012) is provided in Table 4. Among the treated population 36.2% and 10.5% of patients discontinued treatment in the sorafenib and placebo arms, respectively. The majority of patients in the sorafenib arm discontinued treatment due to disease progression or adverse events while in the placebo arm the majority of treatment discontinuations were due to patient withdrawal. All other reasons for treatment discontinuation were similar among the two arms. Sorafenib was made available, via an extension program or other mechanism, to patients who continue to show benefit after the study endpoint, until disease progression or unacceptable toxicity.[6] While 43% and 78.1% of patients in the sorafenib and placebo arms, respectively were assigned to open label sorafenib following the primary analysis period, 26.5 and 71.4% received sorafenib in the open label period. Only results from the double blind period of the study are reported here.

Table 4. Patient disposition at the time of the primary data analysis (Aug 2012).[1]		
	Sorafenib, n=209*	**Placebo, n=210†**
Patients treated, n (%)	**n=207 (100%)**	**n=209 (100%)**
Assigned to open label sorafenib following progression	89 (43.0%)	164 (78.1%)
Ongoing with double blind sorafenib	43 (20.8%)	23 (11.0%)
Discontinued double blind treatment	75 (36.2%)	22 (10.5%)
Disease progression	21 (10.1%)	3 (1.4%)
Adverse events	31 (15.0%)	5 (2.4%)
Related to study drug	24 (11.6%)	2 (1.0%)

Table 4. Patient disposition at the time of the primary data analysis (Aug 2012).[1]		
	Sorafenib, n=209*	Placebo, n=210†
Unrelated to study drug	4 (1.9%)	2 (1.0%)
Unknown determination of which AE lead to a discontinuation	3 (1.5%)	1 (0.5%)
Investigator decision	1 (0.5%)	1 (0.5%)
Died	6 (2.9%)	2 (1.0%)
Withdrawal by patient	12 (5.8%)	10 (4.8%)
Lost to follow-up	3 (1.5%)	1 (0.5%)
Non-compliance	1 (0.5%)	0
Notes:* Two patients were randomized twice by mistake and were not included in the ITT population; therefore, the total number of patients in the sorafenib group was 207 † one patient never received placebo		

e) Limitations/Sources of Bias

- At the primary analysis of progression-free survival, 150 (71.4%) of 209 placebo patients who experienced progression, subsequently enrolled in an open-label study of sorafenib. Due to the high rate of crossover to active therapy, results for overall survival are likely to be biased against sorafenib. Corrections were however performed to account for confounding. Likewise, safety assessments are likely to be biased against sorafenib due to the longer median duration on sorafenib compared with placebo.
- The study was funded by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals (an Amgen subsidiary). Additionally, Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals funded and participated in the design of the study, collection and analysis of data, and interpretation of results.[1]
- Due to the nature of the intervention used, a tyrosine kinase inhibitor vs. placebo, the blinding of the study could have been compromised. Adverse events associated with tyrosine kinase inhibitors are well known and can be identified by study personnel. The assessment of results was however conducted by a blinded independent review committee thus limiting the potential for bias in tumour assessments.
- There is no active treatment in the comparator arm.
- PFS was the primary outcome in the study. However, it is not clear if there is an association between PFS and overall survival in differentiated thyroid cancer.
- Health related quality of life was an exploratory analysis in the study and is therefore subject to bias. Patients who are asymptomatic generally have a good quality of life and treatment with sorafenib is associated with toxicity and decrease in quality of life, therefore the design of a study to assess differences in quality of life would have been important. The study also did not report the proportion of patients who are symptomatic and asymptomatic.
- The study protocol was amended to increase the planned number of patients entered into the trial from 380 (190 subjects in each arm) to 420. The submitter clarified during the Checkpoint meeting that there was a higher-than-originally expected discrepancy between local and central assessments of PFS. In order to obtain the planned 267 events, it was necessary to increase the sample size of the DECISION trial from 380 to 420 randomized patients.

- The study was designed to assess the efficacy and safety of sorafenib in both locally advanced and metastatic patients with DTC. The study however included mostly patients with metastatic disease (96%) and therefore, the efficacy and safety of sorafenib in the locally advanced population is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 5. Key efficacy and harms outcomes reported at the primary analysis for the DECISION study comparing sorafenib vs. placebo in patients with locally advanced or metastatic differentiated thyroid cancer.[1]

Efficacy Outcomes

Analysis date	Study arms	OS, median (mos)	PFS, median (mos)	ORR (%)
Primary analysis (August, 2012)	Sorafenib, n=207	Not reached	10.8	12.2
	Placebo, n=209	Not reached	5.8	0.5
		HR 0.80 95%CI 0.54 to 1.19 P=0.14 (one sided)	HR 0.59 95%CI 0.45 to 0.76 P<0.0001	

Harms Outcomes

	Sorafenib, n=207	Placebo, n=209
Treatment emergent deaths, n (%)	12 (5.8)	6 (2.9)
Treatment related deaths	1 (<1)	1 (<1)
Grade 3/4 TEAE's typically associated with TKI use, n (%)		
Fatigue	11 (5.3)/1 (0.5)	3 (1.4)/0
Diarrhea	11 (5.3)/1 (0.5)	2 (1)/0
Hand and foot syndrome	42 (20.3)/--	0/--
Oral mucositis (functional/symptomatic)	1 (0.5)/1 (0.5)	0/0
Hypertension	20 (9.7)/0	5 (2.4)/0
Serum TSH increase (MedDRA)*	0/0	0/0
Hypocalcaemia	12 (5.8)/7 (3.4)	1 (0.5)/2 (1.0)
Dose Reduction, n (%)	133 (64.3)	19 (9.1)
Dose Interruption, n (%)	137 (66.2)	54 (25.8)
Withdrawal due to adverse events, n (%)	39 (18.8)	8 (3.8)

Notes: 95%CI= 95% confidence interval; HR=hazard ratio with HR<1 favouring sorafenib; mos=months; n=number of patients; NR=not reported; OS=overall survival; PFS=progression-free survival; TEAE: treatment emergent adverse event; TSH: thyroid stimulating hormone; MedDRA: Medical Dictionary for Regulatory Activities.

*TSH concentrations higher than 0.5mIU/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.

Efficacy Outcomes

Overall Survival[1]

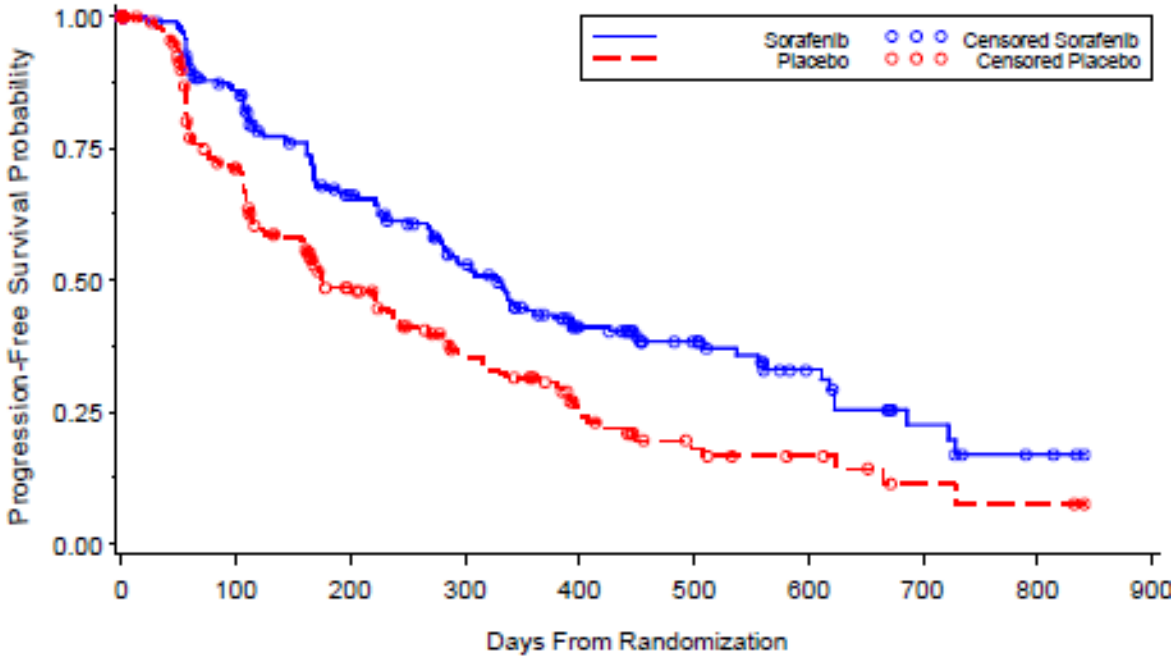
OS was defined as the time from the date of randomization to the date of death from any cause.[7] The DECISION study did not report significant differences in overall survival between the two arms (HR: 0.80 95%CI 0.54-1.19 p=0.14). At the primary analysis date median overall survival had not been reached. Additionally, 150 (71.4%) of patients in the placebo arm crossed over to receive open label sorafenib following progression. A 9 month updated analysis from May 31, 2013 showed that 75% of patients had crossed over to open label sorafenib and a total of 138 events (66 vs. 72 in the sorafenib vs. placebo arms, respectively) had occurred with the median OS still not reached and no demonstrated statistically significant differences in OS between arms.[8] It is notable that adjustments were done to account for confounding due to cross over during the primary and updated analysis. Cross-over adjustments did not demonstrate any significant differences between arms at both analysis dates.

Progression free survival—Primary Outcome

Progression-free survival was defined as the time from randomization to date of first observed disease progression (radiological as determined by central radiological review or clinical progression due to bone lesions that required external radiation, whichever was earlier) or death (due to any cause) if it occurred before progression was documented.[7] The DECISION study met its primary endpoint and showed a statistically significant longer independently assessed PFS in favour of the sorafenib arm with a 41% reduction in the risk of progression or death during the double blind period. At the time of the analysis, 250 PFS events (progressive disease or death) had occurred with 113 vs. 137 events in the sorafenib vs. placebo, respectively.[2] Median time from randomization to last known follow up was 16.2 months (0.03-33.2 months).[1] The median PFS was 10.8 vs. 5.8 months in the two arms respectively (HR 0.59 95%CI 0.45-0.76 p<0.0001). Investigator-assessed PFS was similar to the independently assessed PFS results. While efficacy outcomes in patients with symptomatic vs. asymptomatic disease was identified as a subgroup of interest, data was not collected on the presence or absence of thyroid cancer related symptoms in the case report forms at baseline, during the study or at the time of progression.[2]

A total of 94 and 73 patients were censored in the sorafenib and placebo arms for the primary analysis of PFS, respectively. Among these 72 (34.8%) and 64 (30.5%) were censored due to no progression or death up to the last tumour assessment (even though tumour assessment was performed post baseline) in the sorafenib and placebo arms, respectively.[2] The submitter clarified through the Checkpoint meeting that the remaining 22 and 9 patients that were censored in the sorafenib and placebo arms were censored for the following reasons: no post baseline tumour assessment and no clinical progression or death (13 and 7), death occurring more than 16+1 weeks after last tumour assessment (9 and 1), and progression after two consecutive missed or non-evaluable assessment (16+1 weeks) (0 and 1), respectively in the sorafenib and placebo arms.[33]

Figure 1. Progression free survival Kaplan-Meier curves from the DECISION study based upon August 2012 primary analysis[2]



Patients at Risk

Sorafenib	207	157	110	81	49	33	18	8	3
Placebo	210	133	76	47	25	12	8	3	2

Source: EPAR report[2]

Objective Response Rate

The objective response rate, defined as the proportion of patients whose best response was CR or PR that was achieved before or at the date of unblinding, was 12.2% vs. 0.5% in the sorafenib and placebo arms respectively.[1] There was an 11.8% difference between the two arms (95% CI: 7.0% - 16.5%) and this was a statistically significant difference ($p<0.0001$) using central assessment.[2]

Quality of Life[3]

The majority of patients (96%) completed the questionnaires. Baseline FACT-G scores were similar between the sorafenib and placebo arms (81 ± 15 vs. 82 ± 14; mean ± SD, respectively) and similar to a normative adult cancer population. Total FACT-G scores in the sorafenib arm were lower at first assessment (76 ± 15; cycle 2, day 1) and remained steady thereafter. The majority of changes in FACT-G score appears to be driven by changed in the subscale of physical well-being and functional well-being while social/family and emotional well-being were more similar across the two arms (Table 6). Longitudinal estimates using mixed linear modelling showed that the FACT-G total score was 3.45 points lower in the sorafenib arm compared to the placebo arm, a statistically significant ($p=0.0006$) difference.[3] Based on the accepted minimal clinically important difference (MCID) for FACT-G assessment, this was considered to be a clinically meaningful difference. While MCID differences were not observed,

statistically significant decreases were also measured in the EQ-5D index (-0.07, p<0.0001) and VAS scale (-6.75; p<0.0001) suggesting that sorafenib results in lower quality of life compared to placebo.[3]

Table 6. Analysis of treatment effect on FACT-G subscale and total scores during the double-blind period, time-adjusted AUC (PROAS)[2]

	Sorafenib			Placebo		
Subscale	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Physical well-being	194	20.548	4.502	195	23.033	4.479
Social/family well-being	194	21.477	4.836	195	21.751	4.446
Emotional well-being	195	17.678	4.445	195	17.832	3.707
Functional well-being	196	17.196	5.759	195	18.372	5.563
FACT-G total score	**193**	**76.885**	**15.271**	**194**	**80.967**	**13.934**

AUC = area under the curve; FACT-G = Functional Assessment of Cancer Therapy – General; PROAS = patient reported outcomes analysis set; SD = standard deviation.

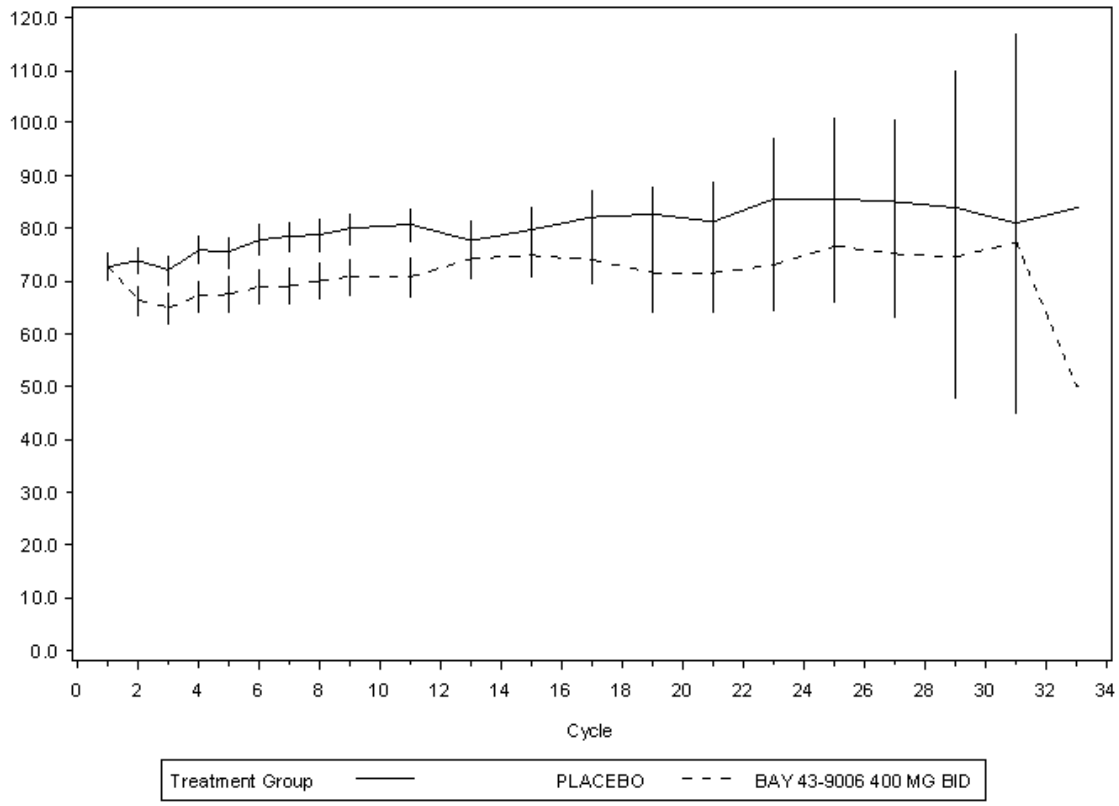
Source: EPAR report[2]

Table 7: Pattern in changes for FACT-G total scores in patients randomized to receive sorafenib.[2]

Pattern	Subjects N=197 (100%)
Improvement in score	30 (15%)
Improvement only	12[h] (6%)
Improvement then decrease	18[i] (9%)
No change in score	52[g] (26%)
Decrease in score	107 (54%)
Gradual decrease	30[a] (15%)
Decrease then improvement	33[b] (17%)
Decrease then leveling off	12[c] (6%)
Decrease then improvement then decrease	16[d] (8%)
Severe decrease	11[e] (6%)
Late decrease	5[f] (3%)
No pattern could be identified or FACT-G total score is missing	8[j] (4%)

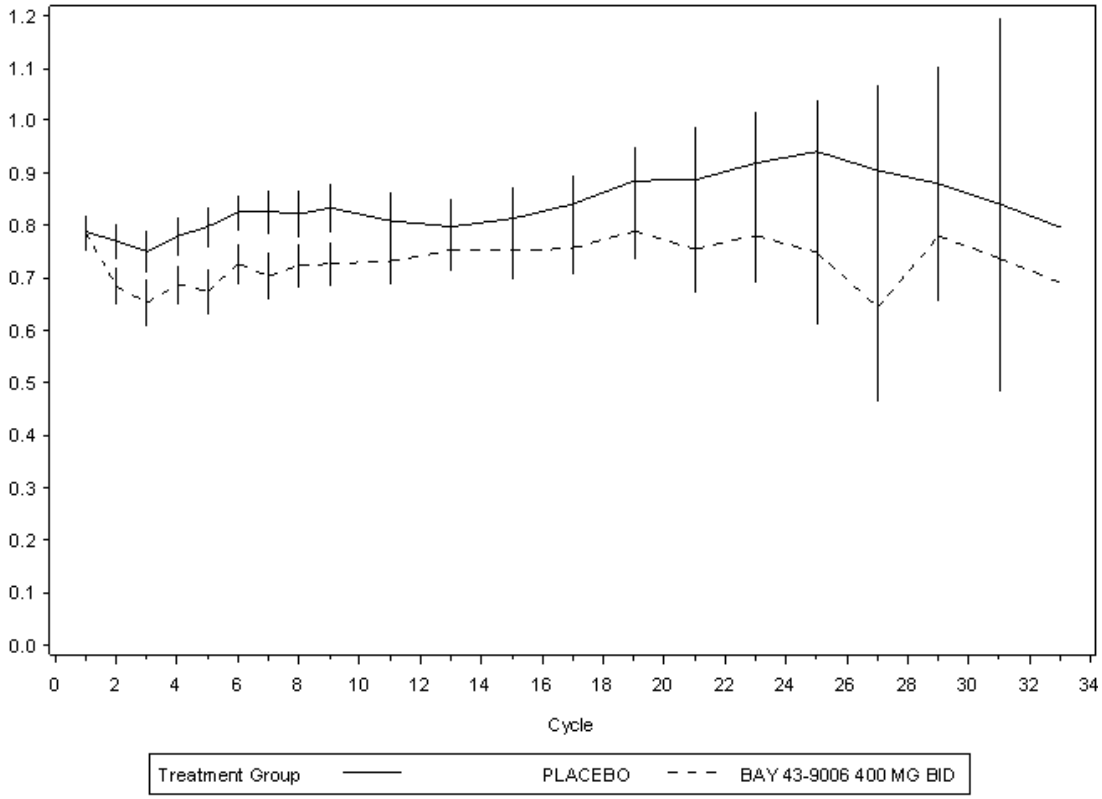
Source: EPAR report[2]

Figure 2. EQ-5D VAS questionnaire – means and 95% confidence intervals (PROAS)[2]



Source: EPAR report[2]

Figure 3. EQ-5D Index questionnaire – means and 95% confidence interval (PROAS)[2]



Source: EPAR report[2]

Harms Outcomes[1]

Deaths

Twelve treatment-emergent deaths (occurring up to 30 days from discontinuation of therapy) occurred in the sorafenib group and 6 in the placebo group. In the sorafenib group, 7 deaths were attributable to underlying disease, 2 to unknown causes, and 1 each to lung infection, chronic obstructive lung disease, and myocardial infarction. In the placebo group, 4 deaths were attributable to underlying disease and 1 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).

Grade 3 or higher Treatment Emergent Adverse Events

More patients in the sorafenib vs. placebo arms experienced at least one grade 3 treatment emergent adverse events (TEAE), 52.7% vs. 23.4% respectively (Table 8). For patients receiving sorafenib, about 60% experienced grade 3/4 adverse events or adverse drug reactions on treatment.[2] Among the adverse events typically associated with the use of tyrosine kinase inhibitors, grade 3 TEAE's were reported in 5.3% vs. 1.4%, 5.3% vs. 1%, 20.3% vs. 0%, 0.5% vs. 0% and 9.7% vs. 2.4% of patients for fatigue, diarrhea, hand and foot syndrome, oral mucositis and hypertension (Table 8). Grade 3 hypocalcaemia also occurred in 5.8% of patients treated with sorafenib.

Serious Adverse events

Serious adverse events occurred in 37.2% and 26.3% of patients in the sorafenib and placebo arms, respectively. Serious adverse events that occurred in 2% or more of patients receiving sorafenib vs. placebo were secondary malignancy (4.3% vs. 1.9%), dyspnoea (3.4% vs. 2.9%), and pleural effusion (2.9% vs. 1.9%), respectively. 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.

All Grades Treatment Emergent Adverse Events (TEAE's)

Nearly all patients experienced at least one treatment emergent adverse event (TEAE) in both arms (Table 8). Adverse events were mainly grades 1 or 2 (Table 8) and were reported to have occurred mostly early in treatment (data not shown). Overall, patients in the sorafenib arm experienced more TEAEs than those in the placebo arm. For adverse events typically associated with the use of tyrosine kinase inhibitors: fatigue (49.8% vs. 25.4%), diarrhea (68.6% vs. 15.3%), hand and foot syndrome (76.3% vs. 9.6%), oral mucositis (23.2% vs. 3.3%) and hypertension (40.6% vs. 12.4%), occurred in the sorafenib vs. placebo arms, respectively. Any grade increase in serum TSH levels above 0.5mIU/L was recorded as an AE in 33.3% of patients in the sorafenib arm while grade 3 or 4 increases were not observed. Any grades hypocalcaemia was measured in 18.8% vs. 4.8% of patients in the sorafenib vs. placebo arms respectively, while grade 3 and 4 hypocalcaemia was measured in 5.8% and 3.4% of patients in the sorafenib arm, respectively and was under 1% in the placebo arms.

Table 8. Adverse events and Treatment emergent adverse events.[1,2]

	Sorafenib, n=207		Placebo, n=209	
	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)
All TEAE's or grade 3/4 TEAEs[2]	204 (98.6%)	109 (52.7)/ 24 (11.6)	183 (87.6%)	49 (23.4)/ 14 (6.7)
Treatment emergent adverse events occurring in at least 10% of patients.[1]				
Fatigue	103 (49.8)	11 (5.3)/1 (0.5)	53 (25.4)	3 (1.4)/0
Diarrhea	142 (68.6)	11 (5.3)/1 (0.5)	32 (15.3)	2 (1)/0
Hand and foot syndrome	158 (76.3)	42 (20.3)/--	20 (9.6)	0/--
Oral mucositis (functional/symptomatic)	48 (23.2)	1 (0.5)/1 (0.5)	7 (3.3)	0/0
Hypertension	84 (40.6)	20 (9.7)/0	26 (12.4)	5 (2.4)/0
Alopecia	139 (67.1)	--/--	16 (7.7)	--/--
Rash Desquamation	104 (50.2)	10 (4.8)/0	24 (11.5)	0/0
Weight Loss	97 (46.9)	12 (5.8)/--	29 (13.9)	2 (1.0)/--
Anorexia	66 (31.9)	5 (2.4)/0	10 (4.8)	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)	0/0	32 (15.3)	0/--

Table 8. Adverse events and Treatment emergent adverse events.[1,2]				
	Sorafenib, n=207		Placebo, n=209	
	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)
All TEAE's or grade 3/4 TEAEs[2]	204 (98.6%)	109 (52.7)/ 24 (11.6)	183 (87.6%)	49 (23.4)/ 14 (6.7)
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 (1.5)/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
All serious adverse events and serious adverse event occurring in at least 2% of patients				
All SAEs	77 (37.2)		55 (26.3)	
In at least 2% of patients				
Secondary malignancies	9 (4.3)		4 (1.9)	
Dyspnoea	7 (3.4)		6 (2.9)	
Pleural effusion	6 (2.9)		4 (1.9)	

Notes: SAE: serious adverse events; TSH: thyroid stimulating hormone; MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment related adverse event

*TSH concentrations higher than 0.5mIU/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.

Dose reductions and dose interruptions

More patients in the sorafenib vs. placebo arm experienced dose reductions (64.3% vs. 9.1%, respectively) and interruptions (66.2% vs. 25.8%, respectively) due to adverse events. (Table 9) In the sorafenib arm hand and foot reactions were the most common cause for dose interruptions (26.6%) and reductions (33.8%).[1] Hand and foot reactions were generally managed with dose reductions and the majority of patients were able to have their dose

escalated after initial reduction.[2] Dose reductions in the sorafenib arm typically started during cycle 1 with 35% of patients requiring a reduction at cycle 1. Dose reductions increased during subsequent cycles being required in 50-60% of patients thereafter.[2,11] Dose interruptions were the highest during cycles 1 and 2 with 37% and 26% of patients requiring a dose interruption. By cycle 5 of treatment, dose interruptions were required in <10% of patients.[2,11]

Table 9. Dose reduction, interruptions and withdrawals occurring in >5% of patients[2]		
	Sorafenib, n=207	Placebo, n=209
All Dose Interruption, n (%)	**137 (66.2%)**	**54 (25.8%)**
Fatigue *	12 (5.8)	2 (1.0)
Rash *	12 (5.8)	0
Hand and foot syndrome * (functional/symptomatic)	54 (26.1)	0
Hypertension *	16 (7.7)	3 (1.4)
All Dose Reduction, n (%)	**133 (64.3%)**	**19 (9.1%)**
Weight decrease *	13 (6.3)	1 (0.5)
Rash *	12 (5.8)	0
Hand and foot syndrome * (functional/symptomatic)	69 (33.3)	1 (0.5)
Hypertension *	12 (5.8)	1 (0.5)
All Withdrawals, n (%)	**39 (18.8%)**	**8 (3.8%)**
Hand and foot syndrome *	11 (5.3)	0

Withdrawal due to adverse events

Treatment emergent adverse events resulting in permanent discontinuation of therapy occurred more in the sorafenib vs. placebo arms (18.8% vs. 3.8%, respectively). The most common cause for permanent discontinuation in the sorafenib arm was hand and foot skin reactions occurring in 5% of patients.

Table 10. Adverse events leading to permanent discontinuation in patients treated with Sorafenib[2]

System Order Class Preferred term	Double-blind Treatment	
	Sorafenib	Placebo
	N=207 n (%)	N=209 n (%)
Any AE Leading to Discontinuation	**39 (18.8)**	**8 (3.8)**
Skin and Subcutaneous Tissue Disorders	**15 (7.2)**	**0**
Dry skin	1 (0.5)	0
Palmar-plantar erythrodysaesthesia syndrome	11 (5.3)	0
Rash	3 (1.4)	0
Respiratory, Thoracic and Mediastinal disorders	**8 (3.9)**	**1 (0.5)**
Dyspnea	2 (1.0)	1 (0.5)
Epistaxis	2 (1.0)	0
Pleural effusion	2 (1.0)	0
Investigations	**7 (3.4)**	**2 (1.0)**
Alanine aminotransferase increased	2 (1.0)	0
Weight decreased	1 (0.5)	2 (1.0)
Gastrointestinal Disorders	**5 (2.4)**	**1 (0.5)**
Diarrhea	2 (1.0)	0
General Disorders and Administration Site Conditions	**4 (1.9)**	**0**
Fatigue	2 (1.0)	0
General physical health deterioration	1 (0.5)	0
Musculoskeletal and Connective Tissue Disorders	**3 (1.4)**	**0**
Bone pain	2 (1.0)	0

Source: EPAR report[2]

6.4 Ongoing Trials

No ongoing and/or unreported trials were identified that would have met the inclusion criteria for the systematic review.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Endocrine Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on sorafenib (Nexavar) for differentiated thyroid cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Endocrine Clinical Guidance Panel is comprised of three medical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature search via Wiley platform

Database(s): **Embase** 1974 to present**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Date: December 18, 2014

Embase, Ovid MEDLINE(R)			
#	**Searches**	**Results**	**Search Type**
1	(sorafenib* or Nexavar* or Bay-43-9006 or BAY43-9006 or BAY439006 or BAY-439006 or BAY-54-9085 or BAY54-9085 or BAY-549085 or BAY549085 or BAY-545-9085 or BAY545-9085 or BAY5459085 or BAY-5459085 or HSDB-5739 or HSDB5739).ti,ab,ot,sh,hw,rn,nm.	21109	Advanced
2	(284461-73-0 or 475207-59-1).rn,nm.	12852	Advanced
3	or/1-2	21109	Advanced
4	Thyroid Neoplasms/	53844	Advanced
5	thyroid*.ti,ab.	327508	Advanced
6	DTC.ti,ab.	5911	Advanced
7	or/4-6	337814	Advanced
8	and/3,7	857	Advanced
9	8 use pmez	198	Advanced
10	*sorafenib/	4159	Advanced
11	(sorafenib* or Nexavar* or Bay-43-9006 or BAY43-9006 or BAY439006 or BAY-439006 or BAY-54-9085 or BAY54-9085 or BAY-549085 or BAY549085 or BAY-545-9085 or BAY545-9085 or BAY5459085 or BAY-5459085 or HSDB-5739 or HSDB5739).ti,ab.	11748	Advanced
12	or/10-11	12015	Advanced
13	exp thyroid cancer/	79955	Advanced
14	thyroid*.ti,ab.	327508	Advanced
15	DTC.ti,ab.	5911	Advanced
16	or/13-15	341390	Advanced
17	and/12,16	525	Advanced

18	17 use oemezd	350	Advanced
19	or/9,18	548	Advanced
20	remove duplicates from 19	396	Advanced

2. Literature search via PubMed

Query
"sorafenib" [Supplementary Concept] OR sorafenib*[tiab] OR Nexavar*[tiab] OR Bay-43-9006[tiab] OR BAY43-9006[tiab] OR BAY439006[tiab] OR BAY-439006[tiab] OR BAY-54-9085[tiab] OR BAY54-9085[tiab] OR BAY-549085[tiab] OR BAY549085[tiab] OR BAY-545-9085[tiab] OR BAY545-9085[tiab] OR BAY5459085[tiab] OR BAY-5459085[tiab] OR HSDB-5739[tiab] OR HSDB5739tiab] OR 284461-73-0[rn] OR 475207-59-1[rn] AND "Thyroid Neoplasms"[Mesh] OR thyroid*[tiab]

3. Cochrane Central Register of Controlled Trials (Central)

Searched January 2015, similar terms to above

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: nexavar or sorafenib AND thyroid

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: nexavar or sorafenib AND thyroid

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

Search terms: nexavar or sorafenib AND thyroid/ last 5 years

REFERENCES

1. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic diff erentiated thyroid cancer: A randomised, double-blind, phase 3 trial. The Lancet. 2014;384(9940):319-28.

2. European Public Assessment Report (EPAR): Nexavar (sorafenib) [Internet]. London: European Medicines Agency; 2015. [cited 2015 Apr 6]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000690/human_med_000929.jsp

3. Schlumberger M, Jarzab B, Elisei R, Siena S, Bastholt L, De La FC, et al. Phase III randomized, double-blinded, placebocontrolled trial of sorafenib in locally advanced or metastatic patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC)-exploratory analyses of patient-reported outcomes [abstract]. Thyroid. 2013;23:A49-A50.

4. Canadian Cancer Society [Internet]. Toronto: The Society. Thyroid cancer statistics; 2014 [cited 2015 Apr 6]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/thyroid/statistics/?region=on

5. Nexavar (sorafenib) tablets: 200 mg sorafenib (as sorafenib tosylate), multikinase inhibitor [product monograph]. Mississauga (ON): Bayer Inc.; 2014.

6. Brose MS, Nutting CM, Sherman SI, Shong YK, Smit JWA, Reike G, et al. Rationale and design of decision: A double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer. BMC Cancer [Internet]. 2011 [cited 2015 Jan 12];11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3164634/pdf/1471-2407-11-349.pdf

7. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 -. Identifier NCT00984282, A double-blind randomized phase III study evaluating the efficacy and safety of sorafenib compared to placebo in locally advanced/metastatic RAI-refractory differentiated thyroid cancer; 2015 [cited 2015 Apr 6]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00984282

8. Brose MS, Jarzab B, Elisei R, Siena S, Bastholt L, De La FC, et al. Updated overall survival analysis of patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) treated with sorafenib on the phase 3 DECISION trial [abstract]. J Clin Oncol. 2014;32(15 Suppl 1).

9. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015 Jan 1;372(1):30-9.

10. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012 Jul 28;380(9839):358-65.

11. Worden FP, Fassnacht M, Shi Y, Hadjieva T, Bonichon F, Gao M, et al. Safety and tolerability of sorafenib for treatment of locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC): Detailed analyses from the phase III DECISION trial [abstract]. J Clin Oncol. 2014;32(15 Suppl 1).

12. Andrews A. Sorafenib effective in metastatic differentiated thyroid cancer. American Health and Drug Benefits. 2013;6(6 Special issue).

13. Mechcatie E. Sorafenib approved for late-stage thyroid cancer. Oncology Report. 2014;(JAN):3.

14. Pitoia F. Sorafenib: Is a partial response and stabilization of disease greater than 70% a modest response? Endocr Relat Cancer. 2014;21(2):L1-L2.

15. Warpakowski A. Radioiodine-resistant differentiated thyroid cancer: Sorafenib extends progression-free survival. Arzneimitteltherapie. 2014;32(11):341-2.

16. Wendling P. Sorafenib slows progression of advanced thyroid cancer. Oncology Report. 2013;(JUL):11-2.

17. Brose MS, Schlumberger M, Pena C, Kappeler C. Sorafenib for patients with differentiated thyroid cancer--authors' reply. Lancet. 2015 Jan 17;385(9964):228-9.

18. Huillard O, Blanchet B, Durand JP, Goldwasser F. Sorafenib for patients with differentiated thyroid cancer. Lancet. 2015 Jan 17;385(9964):227.

19. Boudou-Rouquette P, Thomas-Schoemann A, Bellesoeur A, Goldwasser F. Sorafenib for patients with differentiated thyroid cancer. Lancet. 2015 Jan 17;385(9964):227-8.

20. Dadu R, Devine C, Hernandez M, Busaidy N, Waguespack SG, Hu MI, et al. Survival and efficacy of salvage tyrosine kinase inhibitors (TKIS) after first line sorafenib (SOR) failure in patients with advanced differentiated thyroid cancer (DTC) [abstract]. Thyroid. 2013;23:A48.

21. Hasskarl J. Sorafenib. Recent Results Cancer Res. 2010;184:61-70.

22. Park C, Perini J, Farmer RW, Fancy T, Monga M, Remick SC. Sorafenib and thyroid cancer. Expert Review of Endocrinology and Metabolism. 2014;9(6):561-70.

23. Wright JJ, Zerivitz K, Gravell A. Current clinical trials of BAY 43-9006, Part 1. Oncology. 2005;19(4):499-502.

24. Bockisch A, Brose MS, Nutting C, Jarzab B, Elisei R, Siena S, et al. Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer (DTC): The phase III DECISION trial [abstract]. Experimental and Clinical Endocrinology and Diabetes. 2014;122(3).

25. Paschke R, Brose MS, Nutting C, Jarzab BJ, Elisei R, Siena S, et al. Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase 3 DECISION trial [abstract]. Onkologie. 2013;36:184.

26. Brose MS, Nutting C, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase III DECISION trial [abstract]. J Clin Oncol. 2013;31(18 Suppl 1).

27. Kroiss M, Worden F, Shi J, Hadjieva T, Bonichon F, Gao M, et al. Safety and tolerability of sorafenib for treatment of locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC): Detailed analyses from the phase III DECISION trial [abstract]. Oncology Research and Treatment. 2014;37:269.

28. Paschke R, Brose MS, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Updated overall survival analysis of patients with locally advanced or metastatic radioactive iodine-refractory

differentiated thyroid cancer (RAI-rDTC) treated with sorafenib on the phase 3 DECISION trial [abstract]. Oncology Research and Treatment. 2014;37(Suppl 5):120.

29. Brose MS, Nutting C, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase 3 decision trial [abstract]. Oncology Research and Treatment. 2014;37 Suppl 1:130-1.

30. Bastholt L, Brose MS, Jarzab B, Schlumberger M, Siena S, De La Fouchardiere C, et al. Population PK modeling and exposure-response analyses of sorafenib in patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) in the phase III DECISION trial [abstract]. J Clin Oncol. 2014;32(15 Suppl 1):6061.

31. Brose MS, Nutting C, Shong YK, Sherman SI, Smit JWA, Chung J, et al. Association between tumor BRAF and RAS mutation status and clinical outcomes in patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) randomized to sorafenib or placebo: Sub-analysis of the phase III DECISION trial [abstract]. Eur J Cancer. 2013;49(Suppl 2):S745.

32. Paschke R, Brose MS, Nutting C, Shong YK, Sherman SI, Smit JWA, et al. Association between tumor BRAF and RAS mutation status and clinical outcomes in patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) randomized to sorafenib or placebo: Sub-analysis of the phase III DECISION trial [abstract]. Experimental and Clinical Endocrinology and Diabetes. 2014;122(3):OP7_37.

33. Bayer Inc. response to request for additional information for Nexavar pCODR review [internal manufacturer's report]. Mississauga (ON): Bayer Inc.; 2015.