

## 6.2 SORAFENIB, 200MG TABLET, NEXAVAR<sup>®</sup>, BAYER AUSTRALIA LTD

### 1 Purpose of Application

- 1.1 The submission seeks a Section 85, Authority Required listing for sorafenib for the treatment of locally advanced or metastatic, differentiated thyroid cancer that is refractory to radioactive iodine.

### 2 Requested listing

#### 2.1

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SORAFENIB Tablet, 200mg, 60 tablets	2	2	Nexavar	Bayer Australia Ltd

#### Section 85 Authority required

Treatment for patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma (DTC) refractory to radioactive iodine.

- 2.2 Listing is requested on the basis of a cost-utility analysis versus best supportive care.
- 2.3 The ESC considered that the proposed restriction for sorafenib should include a definition for 'refractory to radioactive iodine' (RAI-R) that aligns with the definition used in the DECISION trial. The sponsor indicated in the pre-PBAC response that they were agreeable to the inclusion of the definition in the restriction.
- 2.4 Further, the ESC considered that the restriction for sorafenib should limit continuing PBS subsidy to patients who have stable or responding disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. While the DECISION trial allowed use of sorafenib post-progression during the open-label phase, the RECIST criteria were used in the trial to determine if progression had occurred.
- 2.5 The PBAC considered the following with regard to the restriction:
- That the patient must have thyroid stage III or IV (since only 3.8% of patients in the sorafenib arm of the trial had thyroid stage I or II)
  - That "locally advanced" be removed and define the metastases as "distant"
  - A definition for RAI-R, i.e.
    - A lesion without iodine uptake on a radioactive iodine (RAI) scan, or
    - Receiving cumulative RAI  $\geq$  600 mCi, or
    - Experiencing a progression after a RAI treatment within 16 months of enrolment, or
    - After two RAI treatments within 16 months of each other
  - That the patient has had thyroid stimulating hormone adequately repressed
  - That patients must have symptomatic progressive disease prior to treatment
  - The PBAC invited comments from the sponsor regarding whether RECIST or thyroglobulin levels would be used to detect disease progression whilst on sorafenib. In clinical practice, PBAC noted that thyroglobulin levels rather than RECIST are used (except in the presence of anti-thyroglobulin antibodies).

### **3 Background**

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, sorafenib was registered for the indications: for the treatment of patients with advanced hepatocellular carcinoma, for the treatment of patients with advanced renal cell carcinoma, and for the treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine.
- 3.2 Sorafenib is not listed on the PBS for the treatment of advanced renal cell carcinoma. Submissions were rejected in November 2006 and November 2008 for first-line treatment of advanced RCC; and in November 2012 and November 2013 for second-line treatment.
- 3.3 Sorafenib is currently listed on the PBS for the treatment of advanced hepatocellular carcinoma (recommended at the July 2008 PBAC meeting).
- 3.4 The PBAC has not previously considered sorafenib for this indication.

### **4 Clinical place for the proposed therapy**

- 4.1 Thyroid cancer generally has a very good prognosis with treatment. However, patients with locally advanced or distant metastatic differentiated thyroid cancer who fail to respond to radioactive iodine, have a survival of only 2.5 to 3.5 years. There is no active treatment currently available for this group of patients.
- 4.2 The estimated median survival time of 2.5 to 3.5 years was quoted from the submission. The Pre-Sub-Committee Response (PSCR) stated that this was based on 'limited available historical epidemiological evidence in patients receiving standard of care' (p4).
- 4.3 The submission proposes sorafenib be used in patients who: progress after treatment with radioactive iodine within 16 months of treatment; progress following treatment with two or more RAI treatments that were within 16 months of each other; progress after a cumulative dose of RAI  $\geq 600\text{mCi}$ ; or in patients who have no uptake of iodine on a radioactive iodine scan.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **5 Comparator**

- 5.1 The submission nominated best supportive care (placebo) as the comparator. The submission argued that no effective treatments are available, with cytotoxic chemotherapy achieving low response rates that may not be durable and being associated with frequent side-effects.
- 5.2 The ESC considered that Best Supportive Care (BSC) was the appropriate comparator.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **6 Consideration of the evidence**

#### ***Sponsor hearing***

6.1 There was no hearing for this item.

**Consumer comments**

6.2 The PBAC noted and welcomed the input from individuals (16), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with sorafenib including slowing down the disease and need for affordable treatment.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Clinical trials**

6.3 The submission presented the results of one trial, DECISION. This was a randomised double-blind trial of 417 patients that compared sorafenib to placebo plus BSC.

6.4 Details of the DECISION trial are presented in Tables 1 and 2.

**Key trial presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
DECISION	Clinical Study Report No. A57578. A double-blind, randomized, phase III trial evaluating the efficacy and safety of sorafenib compared to placebo in patients with locally advanced/ metastatic RAI-refractory, differentiated thyroid cancer. May 2013	Year: 2013 14295 Clinical study report NCT00984282 in clinicaltrials.gov
	Brose MS, Nutting CM, Sherman SI 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. Note: this publication is for the protocol for DECISION. One abstract of the results presented at ASCO has been identified; however a peer reviewed publication was <i>neither presented in the submission nor available at the time that the commentary was prepared.</i>	Year: 2011 BMC Cancer. 2011 Aug 11;11:349.
	<i>However, a peer reviewed publication of the DECISION trial was available at the time of the ESC meeting: Brose M, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial 2014.</i>	Year: 2014 The Lancet, Early Online Publication, 24 April 2014

Source: Table 14, p41 of the submission

**Key features of the included evidence**

Trial	N	Design/ duration <sup>a</sup>	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Sorafenib versus Placebo</b>						
DECISION	417	R, DB, MC 46.1 weeks <sup>a</sup> (sorafenib) 28.3 weeks (placebo)	Low (PFS) <sup>b</sup>	Progressed, radioactive iodine refractory	PFS, OS	PFS OS – adjusted for crossover

DB=double blind; MC=multi-centre; OS=overall survival; PFS=progression-free survival; R=randomised; BSC = best supportive care.

Source: compiled during the evaluation

<sup>a</sup>Median duration of treatment in the double-blind period (data cut-off 31 August 2012). Treatment with sorafenib continued into open label study for 55 patients in the sorafenib arm and overall median duration of treatment at data cut-off 31 August 2012 was 56.9 weeks.

<sup>b</sup>See discussion of risk of bias below.

- 6.5 The extent of attrition bias during the double-blind period of the DECISION trial for Progression Free Survival (PFS) is unclear. As shown in the patient flow diagram below, 75 patients discontinued sorafenib while 22 discontinued placebo. Discontinuations that occurred prior to progression were regarded as censored events. This is inappropriate because patients who discontinue from active therapy have a much higher risk of progression than those who remain on active therapy. Therefore PFS in the sorafenib arm may be over-estimated. If a high number of discontinuations occurred prior to progression (this could not be verified), the risk of bias relating to PFS could be revised to high.
- 6.6 Patients in the placebo arm of the DECISION trial could cross-over to open-label sorafenib upon disease progression or at the end of the double-blind period. Substantial crossover occurred with 150 patients in the placebo arm receiving sorafenib following progression. Thus the overall survival (OS) estimates are confounded. The decision to use sorafenib in the placebo arm following progression was at the investigators' discretion, leading to potential selection bias.

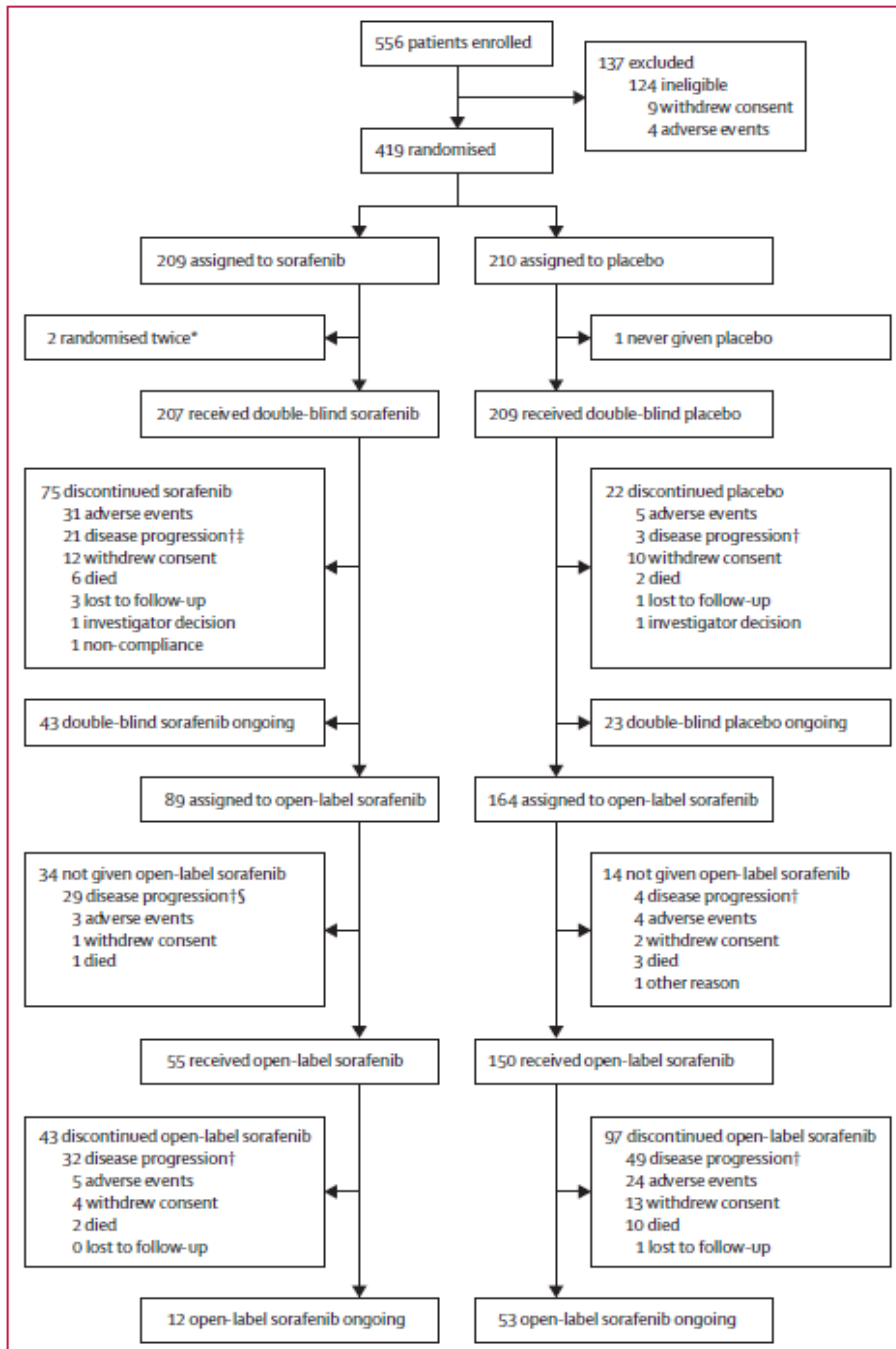


Figure 1: Trial profile

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

**Patient flow diagram**

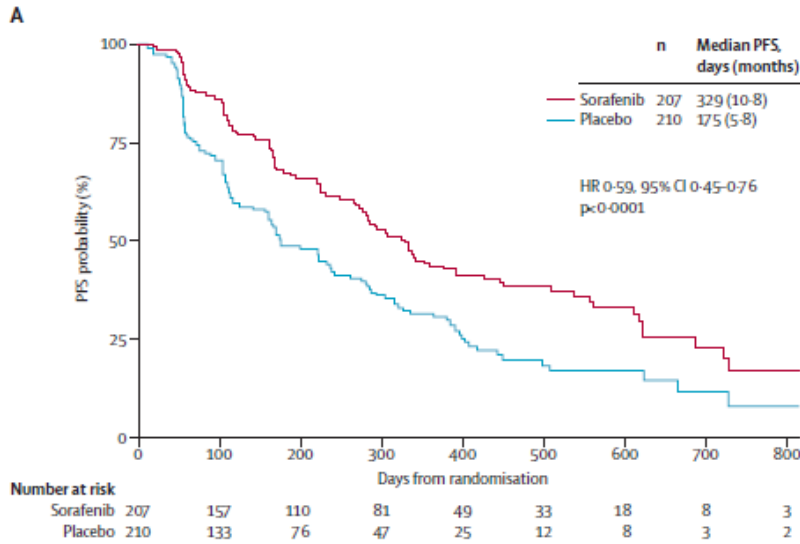
Source: Brose M, et al. *Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial* 2014. The Lancet, Early Online Publication, 24 April 2014)

For more detail on PBAC's view, see section 7 "PBAC outcome"

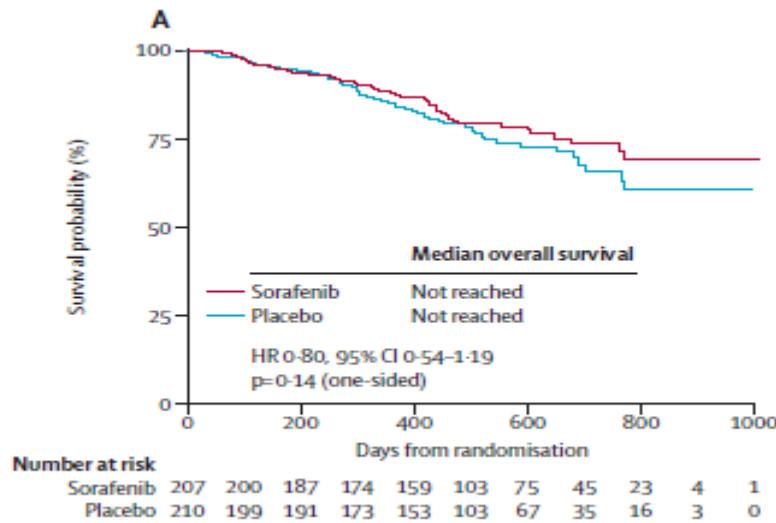
**Comparative effectiveness**

6.7 At time of data cut-off (31 August 2012), median OS had not yet been reached (23.7% of patients had died). Approximately one quarter of patients were still receiving sorafenib at the time of data cut-off.

6.8 The figures below show the Kaplan-Meier curves from the DECISION trial for PFS and OS respectively. A summary of the trial results are in the table below.



*Progression-free survival by central review (intention-to-treat population). Source: Brose M et al, The Lancet, Early Online Publication, 24 April 2014)*



*Kaplan-Meier curve of overall survival Source: Brose M et al, The Lancet, Early Online Publication, 24 April 2014)*

**Results for the DECISION trial (data cut-off 31 August 2012)**

Trial ID	Sorafenib Median survival ± SD (months)	Placebo+BSC Median survival ± SD (months)	Absolute difference (months)	Relative difference HR (95% CI)
PFS – central review	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)	5.0	0.587 (0.454, 0.758)
OS <sup>a</sup>	Median not yet reached		Not calculable	0.802 (0.539, 1.194)

BSC = best supportive care.

Source: Table 34, p75 and Table 38, p81 of the submission

<sup>a</sup> ITT results, not adjusted for cross-over.

- 6.9 The submission attempted to adjust for the substantial cross-over using two statistical methods: the Rank Preserving Structural Failure Time (RPSFT) and the Iterative Parameter Estimation (IPE) method. The ESC considered that RPSFT would provide a more reliable estimate of OS than IPE in this particular data-set. The RPSFT-adjusted hazard ratio for OS is [REDACTED]. However, the difference in OS attributed to sorafenib was ultimately still an estimation. Unlike other cancers, there are no published drug trials for metastatic thyroid cancer show that a given change in PFS would reliably translate into a survival gain.
- 6.10 The DECISION trial allowed continued use of sorafenib post-progression. Therefore OS with sorafenib may be lower in clinical practice if the PBS restriction does not allow post-progression use of sorafenib.
- 6.11 Thus the ESC considered that, based on the trial results and given the high degree of cross-over, it is difficult to tell whether the observed increase in PFS will translate to an increase in OS.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Comparative harms**

- 6.12 Dose modifications were common among patients who received sorafenib (86.0%), and 60% of patients required two or more interruptions to study medication.
- 6.13 More than 70% of patients who received sorafenib experienced at least one Grade 3 reaction or higher compared with 33% of patients who received placebo+BSC.
- 6.14 The most common treatment emergent adverse events associated with sorafenib were hypertension (40.6%), fatigue (49.8%), weight loss (46.9%), hand-foot skin reaction (76.3%) and diarrhoea (68.6%). These were all considerably more common in the sorafenib arm compared with placebo+BSC.
- 6.15 The ESC noted the significant adverse event profile of sorafenib:
- 66.2% of patients had an interruption to therapy in the sorafenib arm, compared with 25.8% in the placebo arm; and
  - 18.8% of patients in the sorafenib arm withdrew due to adverse events compared with 3.8% in the placebo arm.

### **Benefits/harms**

- 6.16 A summary of the comparative benefits and harms for sorafenib versus placebo+BSC is presented below.

Summary of comparative benefits and harms for sorafenib and placebo+BSC

Benefits						
Progression-free survival / Overall survival <sup>a</sup>						
	Sorafenib	PBO+BSC	Absolute Difference	HR (95% CI)		
PFS	113/207	137/210	-	0.587 (0.454, 0.758)		
Median (mths)	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)	5.0	-		
OS	45/207	54/210	-	0.802 (0.539, 1.194)		
Median (mths)	Median not yet reached		Not evaluable			
Trial	Sorafenib	PBO+BSC	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Sorafenib	PBO	
Disease control rate (CR + PR + SD) – per protocol analysis set						
DECISION	169/196	150/201	1.16 (1.05, 1.27)	86.2	74.6	0.12 (0.04, 0.19)
Harms <sup>a</sup>						
	Sorafenib	PBO+BSC	RR (95% CI)	Event rate <sup>b</sup> /100 patients		RD (95% CI)
				Sorafenib	PBO	
Treatment-emergent AE, Grade 3 or higher						
DECISION	147/207	69/209	2.15 (1.74, 2.66)	71.0	33.0	0.38 (0.29, 0.47)
Hand-foot skin reaction, Grade 3 or higher						
DECISION	42/207	0/209	Not calculable	20.3	0	0.20 (0.14, 0.26)
Hypertension, Grade 3 or higher						
DECISION	20/207	5/209	4.04 (1.54, 10.56)	9.7	2.4	0.07 (0.03, 0.12)

<sup>a</sup>PFS and OS are measured to data cut-off of 31 August 2012, at which time median exposure to the drug in the sorafenib arm is 46.1 weeks under double-blind conditions and 56.9 weeks including the open label use of sorafenib. Median exposure to placebo is 28.3 weeks under double-blind conditions.

<sup>b</sup> the proportion of patients who experience at least one adverse event.

Abbreviations: PBO = placebo; RD = risk difference; BSC = best supportive care; RR = risk ratio; AE = adverse event; CR = complete response; PR = partial response; SD = stable disease; PFS = progression free survival; OS = overall survival.

Source: Compiled during the evaluation from Table 34, p75, Table 38, p81, Table 40, p85, Table 51, p96, Table 53, pp99-100.

6.17 **Benefits**

On the basis of the direct evidence presented by the submission, the comparison of sorafenib with placebo resulted in:

- a significant increase in median PFS compared with placebo from 5.8 months (placebo) to 10.8 months (sorafenib): HR 0.587 (0.454 - 0.758). Censoring of patients who ceased sorafenib early due to side effects without progression may bias this result towards sorafenib;
- a significant increase in 'Disease Control', which comprises complete response, partial response and stable disease. The disease control rate was 74.6% in the placebo arm compared with 86.2% in the sorafenib arm: RD 0.12 (0.04-0.19);

6.18 On the basis of the direct evidence presented by the submission, the comparison of sorafenib with placebo did not result in a statistically significant difference in OS for the intention to treat population. The unadjusted HR for OS was 0.80 (0.54 – 1.19). This result may have been affected by the significant crossover (from placebo to open-label sorafenib after disease progression) that occurred in the trial.

6.19 Health-related quality of life data from patients in the trial favoured placebo ( [REDACTED] ) compared with sorafenib [REDACTED].

6.20 **Harms**

On the basis of the direct evidence presented in the submission, for every 100 patients treated with sorafenib in comparison with placebo, approximately:

- 38 additional patients will have at least one Grade 3 or higher Adverse Event (AE).
- 20 additional patients will have Grade 3 or higher Hand-Foot skin reaction.
- 7 additional patients will have Grade 3 or higher hypertension.
- 40 additional patients will have sorafenib treatment interrupted due to AE.
- 55 additional patients will have sorafenib treatment reduced due to AE.
- 15 additional patients will have sorafenib treatment stopped due to AE.

This is based on a period of 10 – 12 months of treatment with sorafenib (compared with 8 – 9 months of observation in the placebo+BSC arm).

- 6.21 The ESC considered that the overall risk-benefit profile of sorafenib was difficult to ascertain given that the trial included extensive crossover; allowed post-progression use of sorafenib, may have inappropriately censored patients who withdrew from treatment; and showed high rates of severe adverse events with sorafenib.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Clinical claim**

- 6.22 The submission describes sorafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo.
- 6.23 The PBAC considered that the claim of superior comparative effectiveness was reasonable provided PFS was considered the only endpoint. The clinical benefit of sorafenib remains uncertain because there was no significant difference in overall survival and the impact of delays in tumour progression on quality of life were not clearly demonstrated.
- 6.24 The PBAC considered that the claim of inferior comparative safety was reasonable.

**Economic analysis**

- 6.25 A modelled economic evaluation (cost-utility analysis) was presented in the submission, based on the clinical claim of superior efficacy and inferior safety of sorafenib compared with best supportive care.
- 6.26 There were three health states in the model – progression-free, progression and death. The model structure is summarised below.

Summary of model structure and rationale

Component	Summary
Time horizon	10 years (130 cycles) in the model base case versus 2 years in the trial
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis
Health states	Progression-free, progressed and death
Cycle length	28 days
Transition probabilities	The proportion of patients in each health state is based on the modelled PFS and OS curves

LYG = life years gained; QALY = quality-adjusted life-year; PFS = progression free survival; OS = overall survival.  
Source: compiled during the evaluation

- 6.27 The key drivers of the model are summarised below.

Key drivers of the model

Description	Method/Value	Impact
OS benefit of sorafenib over BSC	Assuming continued OS benefits throughout modelled time horizon	High, favours sorafenib
	Adjustment of OS in the BSC arm due to cross-over to sorafenib post-progression (methods of adjustment and the 95% CI of hazard ratio in the same adjustment analysis)	
Time horizon	10 years; assumed from 2 years trial duration	High, favours sorafenib
Duration of sorafenib treatment	Average number of cycles of treatment until progression in the DECISION trial (revised base case).	Moderate, favours sorafenib because sorafenib use was also permitted post-progression.
Dose intensity of sorafenib treatment	Dose intensity observed in the DECISION trial, assuming no wastage	Moderate, favours sorafenib
Utilities of health states	Trial-based utility values without disutility associated with continued sorafenib treatment post-progression	Likely to be low, depending on the duration of continued treatment post-progression, favours sorafenib

OS = overall survival; BSC = best supportive care.

Source: compiled during the evaluation

6.28 The model provided in the submission underestimated the cost of sorafenib because it based costs on the average number of cycles of sorafenib during the double-blind period of the DECISION trial. However, some patients had not progressed by the end of the double-blind period. The commentary, PSCR (p5) and ESC agreed that it would be more appropriate to estimate the cost of sorafenib assuming treatment until disease progression. The base case was revised to reflect this.

6.29 The results of the revised economic evaluation are summarised in the table below.

Revised base case (per PSCR) – use of sorafenib until progression

Component	Sorafenib	BSC	Increment
Costs	██████████	██████████	██████████
Lys	██████████	██████████	██████████
QALYs	██████████	██████████	██████████
Incremental cost/LY gained			\$ ██████████
Incremental cost/QALY gained			\$ ██████████

6.30 The updated sensitivity analyses, shown below at 6.41, indicate that the model is most sensitive to the OS estimates - including whether the OS has been adjusted for cross-over, the methods used to adjust patient cross-over and the 95% confidence intervals of the adjusted hazard ratios.

6.31 OS in the BSC arm of the model has been adjusted for cross-over using the RPSFT method, which provides a more favourable estimate than the IPE method or no adjustment. The submission did not provide justification for selecting the RPSFT method. The constant treatment effect assumption has not been supported.

6.32 The ESC considered that the RPSFT method would provide a more reliable estimate of OS than the IPE method in this particular data-set. However, the difference in OS with sorafenib compared with BSC was still difficult to estimate reliably.

6.33 The model is also sensitive to the time horizon, duration and the dose intensity of sorafenib treatment.

- 6.34 The submission's base case assumes a continued OS benefit of sorafenib over BSC over a 10-year time horizon. The ESC considered that this was not reasonable. The model assumes that the hazard ratio for OS (sorafenib versus BSC) will be maintained beyond the duration of therapy and throughout the modelled time horizon. The two extrapolated OS curves do not converge until 15 years. Therefore, the longer the time horizon (until the two OS curves converge), the more favourable the ICER is to sorafenib. Further, the submission has not justified its use of a 10-year time horizon.
- 6.35 The PSCR argues that the 10-year horizon is appropriate because median survival was not reached in either arm of the DECISION trial at 3 years, and the model predicts that approximately 5% of sorafenib patients are still alive at ten years.
- 6.36 The ESC agreed with the commentary and considered that the assumption that 5% of sorafenib patients are still alive at ten years was based on highly favourable assumptions regarding the treatment effect of sorafenib. Further, the ESC noted that the extrapolation of OS was based on small numbers of patients.
- 6.37 The ESC agreed with the commentary that the assumption of a continued treatment effect beyond the duration of therapy seemed implausible. The ESC noted that the model structure does not allow testing of alternative assumptions regarding the convergence of the OS curves. Further, the ESC agreed with the commentary that the 10-year time horizon used in the model seems implausible, and that a 5-year time horizon would be more realistic. The ESC noted that a 5-year time horizon increases the ICER to \$105,000/QALY - \$200,000/QALY.
- 6.38 The DECISION trial allowed continued use of sorafenib post-progression in patients in the sorafenib arm, and the trial's estimate of OS reflects this use. However, the costs of sorafenib use post-progression have not been included in the model. Therefore the revised base case is still inconsistent with the trial and/or clinical practice:
- the OS with sorafenib may be lower in clinical practice if listing was based on use of sorafenib until disease progression only; alternatively
  - if listing allowed use of sorafenib post-progression, the costs of sorafenib use post-progression should be included in the model.
- 6.39 The ESC noted that:
- the estimation of treatment emergent adverse event rates were not able to be validated during evaluation, and the methodology used was unclear in the submission; and
  - the estimates of resource use for managing treatment-emergent adverse events may have been underestimated in the submission because Grade 3 or 4 adverse events are likely to require at least one specialist visit and some may need to be managed in an inpatient setting.
- However, the ESC considered that this would not have a significant impact on the ICER given the adverse event probabilities that were used in the model.
- 6.40 The utility value used in the model for the 'post-progression' health state may bias results against BSC. The utility value used for this health state [REDACTED] was based on a weighted average end-of-treatment index score. This may not have been appropriate because:
- it was based on the small number of patients who remained in the EQ-5D study, particularly in the placebo arm ([REDACTED] patients, compared with [REDACTED] patients remaining in the sorafenib arm);

- the end-of-treatment utility value was markedly lower in the sorafenib arm (■■■■, compared with ■■■■ in BSC arm); and
- the trial allowed post-progression use of sorafenib. The post-progression utility value may not account for the disutility of continuing sorafenib use, further contributing to the inconsistencies between the model presented and the trial.

6.41 The ESC considered that the revised base case was still highly favourable towards sorafenib.

Results of sensitivity analyses – updated to reflect the revised base case

Analyses	Incremental costs	Incremental QALYs	Incremental cost/QALY
Base case (treatment until disease progression)	■■■■	■■■■	■■■■
OS ITT HR (unadjusted for cross-over)	■■■■	■■■■	■■■■
OS HR adjusted using RPSFT (lower limit of 95% CI – ■■■■) - base case HR ■■■■	■■■■	■■■■	■■■■
OS HR adjusted using RPSFT (upper limit of 95% CI- ■■■■) – base case HR ■■■■	■■■■	■■■■	■■■■
OS HR adjusted using IPE – HR ■■■■	■■■■	■■■■	■■■■
OS HR adjusted using IPE – HR ■■■■ (lower limit of 95% CI)	■■■■	■■■■	■■■■
OS HR adjusted using IPE – HR ■■■■ (upper limit of 95% CI)	■■■■	■■■■	■■■■
Time horizon at 5 years	■■■■	■■■■	■■■■
■■■■	■■■■	■■■■	■■■■
■■■■	■■■■	■■■■	■■■■

6.42 The ESC respecified base, using the sensitivity analysis in which treatment is assumed to continue until disease progression and using a median treatment duration as proposed in the Pre-PBAC response of ■■■■, resulted in an ICER of over \$75,000/QALY - \$105,000/QALY. However the PBAC considered that this was uncertain given the sub-optimally defined patient population.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Drug cost/patient/course: \$ ■■■■**

6.43 The submission estimates the costs of sorafenib based on the effective DPMQ of \$■■■■, which is a price for 30 days of treatment. The estimated total drug cost per patient per course is \$■■■■ (undiscounted) per patient based on the extrapolated progression-free survival in the model. This is based on ■■■■ of treatment (the mean duration of treatment until progression) at a dose intensity of ■■■■%.

**Estimated PBS usage & financial implications**

6.44 The submission was considered by the Drug Utilisation Sub-Committee (DUSC). The main issues considered by the DUSC include the following:

- the eligible population of metastatic or locally advanced thyroid cancer was considered to be substantially overestimated (by at least 2 to 3 fold). The submission uses 5-year and 25-year prevalence figures to estimate the eligible population. This overestimates the eligible population because prevalence data would count a large number of patients who no longer have active cancer. Localised thyroid cancer has an excellent prognosis with 5-year relative survival of 98.1%. (Stavrou et al, 2008)
- a mortality approach may be more suitable for this patient population. Age-standardised thyroid cancer mortality has been relatively stable since 1982 (AIHW 2012). The annual number of thyroid cancer deaths from 2000 to 2011 range from 88 to 129 (AIHW 2014).
- The likely duration of treatment is unclear. The financial estimates assume patients will be treated for one year. The treatment duration should be consistent with that in the economic model. The sponsor's Pre-Sub-Committee Response (p5) accepted a treatment duration of [REDACTED] years in the economic model. In practice, sorafenib may be used beyond disease progression.

6.45 The estimated PBS usage and financial implications are presented in the table below.

**Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Treatment eligible patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Uptake among eligible population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Eligible patients receiving treatment	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Average prescription per patient/year	[REDACTED]				
Total utilisation [REDACTED] mg packs) <sup>a</sup>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated net cost to PBS/RPBS</b>					
Net cost to PBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated total net cost</b>					
Net cost to PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Average cost of managing TEAEs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated total cost to Government	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Sensitivity analyses (Net cost to Australian Government)</b>					
Prevalence inflation factor =1	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost of adverse events = \$[REDACTED] per patient	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Figures were re-calculated during the evaluation, correcting for the error in calculating prevalence of locally advanced or metastatic differentiated thyroid carcinoma cases refractory to radioactive iodine

<sup>a</sup> Assuming [REDACTED] packs per patient per year as estimated by the submission.

PBS = Pharmaceutical Benefits Schedule; RPBS = Repatriation Pharmaceutical Benefits Scheme; TEAE = treatment emergent adverse events

Source: Table 87, p159 of the submission and "Attachment 3 - Section E Workbook 10032014.xlsx", worksheet E1-background and assumptions

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## 7 PBAC Outcome

- 7.1 The PBAC rejected the submission for PBS listing of sorafenib for differentiated thyroid carcinoma refractory to radioactive iodine on the basis of high and uncertain cost effectiveness, a sub-optimally defined patient population and uncertain clinical benefit. The PBAC considered that there may be a small population for which this drug may be of benefit - in patients with rapid disease and symptomatic progression where the prognosis is poorer. However the submission did not provide sufficient data to define this group of patients and how they would be identified in clinical practice. The PBAC considered that it was uncertain whether a gain in PFS was clinically meaningful in this type of cancer, in the absence of evidence of a benefit in OS, noting that before progression, health related quality of life data from the trial favoured placebo compared with sorafenib. The PBAC considered that due to the sub-optimally defined nature of the treatment population, and insufficient evidence to support a meaningful clinical benefit, the resulting ICER is high and uncertain.
- 7.2 The PBAC noted that in the past 40 years, the rate of mortality of thyroid cancer has remained constant, however the incidence has dramatically increased. The PBAC noted that this rise was attributed to over-detection of papillary thyroid cancer.
- 7.3 The PBAC noted that there are no drugs listed on the PBS for the requested indication and that there was need for new treatment options for patients with RAI refractory disease in the subgroup of individuals whose disease was recently progressive. The PBAC noted that treatment is not necessarily required for all patients with RAI-R thyroid cancer as the disease can be asymptomatic, indolent and progress slowly. In this regard, the PBAC noted that the clinical trial had very carefully selected patients for inclusion on the key study to ensure only patients in whom treatment was clinically indicated were recruited to the study. The estimated median survival in this group of patients is 2.5 to 3.5 years. The PBAC considered that it is important to define the small population of individuals for whom this drug may be of benefit. This was likely to be the patients with rapid disease and symptomatic progression where the prognosis is poorer. However the submission did not provide sufficient data to define this group of patients and how they would be identified in clinical practice.
- 7.4 The PBAC accepted BSC (placebo) as the appropriate comparator.
- 7.5 The PBAC considered that the result for OS from the key trial in the submission, the DECISION trial, was confounded due to high degree of cross-over. Patients could cross-over to treatment with sorafenib on progression or at the end of the double-blind period; 71.4% of patients from the placebo arm of the trial crossed over to open-label treatment with sorafenib.
- 7.6 The PBAC noted that the outcomes from the DECISION trial showed a gain in PFS of 5 months. Due to the design of the trial, any gain in OS was uncertain. The PBAC noted that most progression was assessed using radiological evaluation, which may have resulted in an overestimation of PFS due to the interval between assessments. The PBAC considered that it was uncertain whether a gain in PFS was clinically meaningful in this type of cancer, in the absence of evidence of a benefit in OS, noting that before progression, health related quality of life data from the trial favoured placebo compared with sorafenib.
- 7.7 The PBAC noted that only a small number of patients were potentially eligible for treatment and in that respect the disease was labelled an “orphan disease”. For this reason, only a small number of expert prescribers may be available in the Australian

setting. The PBAC considered that there would need to be a risk sharing agreement in place to manage potential use of this medicine beyond the restriction and target patient population.

- 7.8 The PBAC accepted that sorafenib has inferior safety compared with BSC (placebo). Noting that in the trial more than 70% of patients who received sorafenib experienced at least one Grade 3 reaction or higher compared with 33% of patients who received BSC (placebo), and that health related quality of life data from patients in the trial favoured placebo compared with sorafenib, the PBAC was concerned about the treatment induced reduction in quality of life, when the clinical significance of a gain in PFS is uncertain.
- 7.9 The PBAC considered that the following model inputs were reasonable:
- time horizon of 10 years
  - costs of the comparator (close to nil)
  - the assumed mean duration of therapy proposed in the Pre-PBAC response of [REDACTED]
  - 0.35 QALYs gained over 5 years and 0.590 QALYs gained over ten years per patient.
- 7.10 The PBAC agreed with the ESC that it was not reasonable to attach utilities to the post-progression health state as it may result in bias against BSC (see 6.40).
- 7.11 The PBAC considered that due to the sub-optimally defined nature of the treatment population, and insufficient evidence to support a meaningful clinical benefit, the resulting ICER is high and uncertain.
- 7.12 The PBAC agreed with the DUSC that the financial estimates were highly uncertain. The submission used 5-year and 25-year prevalence figures to estimate the eligible population which overestimates the eligible treatment population because prevalence data would count a large number of patients who no longer have active cancer or have an indolent form of the disease. The PBAC did not accept that all prevalent cases would merit treatment.
- 7.13 The PBAC considered that a major resubmission would be required to address the Committee's concerns, with particular regard to defining the eligible treatment population and providing evidence of a meaningful clinical benefit with sorafenib in the treatment of RAI-R DTC.
- 7.14 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected.

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

The sponsor had no comment.