5.10 REGORAFENIB
Tablet 40 mg (as monohydrate),
Stivarga®, Bayer Australia Limited.

1 Purpose of Application

1.1 The submission requested a Section 85 Authority Required (STREAMLINED) listing on the Pharmaceutical Benefits Schedule (PBS), for regorafenib for treatment of patients with unresectable hepatocellular carcinoma (HCC) who progressed following treatment with sorafenib. Regorafenib has not been previously considered by the PBAC for this indication.

1.2 The submission presented one head to head clinical trial (RESORCE) which formed the basis of a cost-effectiveness analysis against best supportive care (BSC).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with advanced HCC who have progressed after treatment with sorafenib.
Intervention	Regorafenib 40 mg oral tablet administered four times daily (total 160 mg) at the same time each day for three weeks (21 days) followed by one week off therapy (7 days) to comprise a cycle of four weeks.
Comparator	Best supportive care (BSC).
Outcomes	Primary: OS Secondary: PFS; TTP; ORR; disease control rate (CR + PR + SD); duration of response; duration of stable disease. Tertiary: HRQoL and utility values; pharmacokinetics (PK); biomarker evaluation.
Clinical claim	Regorafenib is superior to BSC for the treatment of advanced HCC, providing a statistically significant and clinically significant increase in OS but associated with a higher incidence of drug related adverse events which were well tolerated and did not significantly impact patient QoL. The clinical claim was supported by the data presented with respect to OS, but may not be supported with respect to the impact of adverse events on QoL.

Abbreviations: BSC= Best supportive care; CR= complete response; HCC= Hepatocellular carcinoma; HRQoL= health related quality of life; ORR= objective tumour response rate; OS= overall survival; PFS= progression free survival; PR= partial response; QoL= quality of life; SD= stable disease; TTP= time to progression
Source: Table 1-1 p. 15 of the submission, Executive summary p. vi of the submission.

2 Requested listing

2.1 The requested restriction is summarised below and is largely consistent with the RESORCE trial.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
REGORAFENIB (STIVARGA®) 40 MG ORAL TABLET, 28	3	2	$[redacted] published $[redacted] effective	Stivarga	Bayer

Category/Program:	Section 85 – Authority required
PBS indication:	HCC in patients who have been previously treated with sorafenib.
Treatment phase:	Initial and continuing
Restriction:	Advanced HCC BCLC Stage C in patients who first received sorafenib treatment at a minimum dose of 400 mg once daily, for a minimum of 20 days
Treatment criteria:	The treatment must be the sole PBS-subsidised therapy for this condition.
Clinical criteria:	Patient must have a WHO PS of 1 or less, must have Child Pugh class A, must have received prior treatment with sorafenib for a minimum of 20 days at a minimum dose of 400 mg QD and patient must have progressed on sorafenib treatment

Abbreviations: HCC= hepatocellular carcinoma; Max= maximum; PS= performance status; QD= once daily; Qty= quantity; WHO= World Health Organization

2.2 The submission proposed a special pricing arrangement (SPA).

2.3 The restriction proposed in the submission may not reflect the eligible population in Australia and may represent differences in the circumstances of use due to:

- Differences in the proposed performance status (PS) criterion. The RESORCE trial enrolled patients with an ECOG ≤ 1 while the current PBS listing for sorafenib is a WHO PS ≤ 2;
- The restriction stated patients should be treated only until progression. Within RESORCE, patients were allowed to continue treatment after progression if the investigator identified a clinical benefit. The Pre-Sub-committee Response (PSCR) proposed the following restriction wording to match the inclusion criteria of the RESORCE trial: 'The patient must only be treated until disease progression OR until no further clinical benefit is observed.' The ESC advised that the more objective criterion 'Patients must only be treated until disease progression' be used in the proposed restriction due to the variation in interpretation of 'clinical benefit' in practice. In the pre-PBAC response the sponsor proposed restriction wording defining clinical benefit based on the RESORCE trial protocol, noting however, that the sponsor is amenable to the wording proposed by ESC. PBAC agreed with ESC that the most appropriate restriction is 'Patients must only be treated until disease progression' as regorafenib is unlikely to be cost effective beyond progression.
- Although the RESORCE trial excluded patients with a known history of HIV, in the pre-PBAC response the sponsor proposed that the eligibility for treatment with regorafenib in this patient population should be managed on a case by case basis with the clinical decision to treat being made between the doctor and the patient. The sponsor noted, however, that it is amenable to include an additional eligibility criterion related to patients HIV status, for example, "Patients must not be HIV immunocompromised".

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

3 Background

Registration status

3.1 Regorafenib was first TGA registered in 2013. The extension of the indication to include treatment of patients with HCC who have been previously treated with sorafenib was effective from 21 December 2017.

Previous PBAC consideration

3.2 This is the first major submission to the PBAC for regorafenib in the treatment of advanced HCC.

3.3 At its July 2014 meeting, the PBAC did not recommend the PBS listing for regorafenib for the treatment of metastatic colorectal cancer on the basis that the observed improvement in comparative effectiveness associated with regorafenib was small and of uncertain clinical significance, especially in the context of the increase in serious adverse effects associated with treatment. The PBAC had considered that the most reliable estimate of the incremental cost-effectiveness ratio for regorafenib compared to best supportive care was unacceptably high, particularly given the small incremental benefit (regorafenib Public Summary Document (PSD), July 2014 PBAC meeting).

3.4 At its March 2015 meeting, the PBAC did not recommend the PBS listing for regorafenib for the treatment of gastrointestinal stromal tumours (GIST) on the basis of uncertain efficacy and cost-effectiveness. The PBAC accepted that regorafenib provides a clinical benefit to patients in terms of PFS, but considered that the adjusted estimates of OS could not be relied upon and the adverse effect profile of regorafenib was not adequately reflected in the model. Given the small clinical benefit due to PFS and the unfavourable safety profile of regorafenib, the PBAC considered that the ICER per QALY gained was highly uncertain (regorafenib PSD, March 2015 meeting).

4 Population and disease

4.1 HCC is the second-commonest cause of cancer-related death worldwide. It is more common in males and approximately 90% of cases are associated with underlying chronic liver disease and liver cirrhosis. The most common aetiologies include chronic hepatitis B and C virus (HBV, HCV), alcohol abuse, and aflatoxin exposure. A reduction in the number of HCV cases progressing to cirrhosis (and potentially HCC) since new antiviral therapies became available on the PBS could reduce the future incidence of HCC. The prevalence of HCC closely mirrors it annual incidence, which is consistent with the presentation of patients with HCC typically at a late stage with poor survival prognosis. The PBAC noted that liver cancer is the 6th most common

cause of cancer death in males and the 9th most common cause of cancer death in females in Australia (AIHW 2017).

4.2 Regorafenib is proposed as a second line treatment of patients who progress following treatment with sorafenib.

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

5 Comparator

5.1 The submission nominated BSC as the main comparator. The RESORCE trial defined BSC as any intervention including concomitant medications, medical procedures, psychotherapy, growth factors, palliative surgery or any other symptomatic therapy - except for anti-tumour agents, anti-neoplastic chemotherapy, hormonal or immunotherapy. The ESC and the PBAC considered that the comparator was appropriate.

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 that no consumer comments were received for this item.

6.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the regorafenib submission. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for regorafenib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[1], based on a comparison with placebo.

Clinical trials

6.4 The submission was based on one head-to-head trial comparing regorafenib with BSC, RESORCE trial (n=573). Details of the trial presented in the submission are provided in the table below. The ESC noted that the PSCR presented the updated overall survival (OS) results (cut-off date Jan 23, 2017) from the RESORCE trial, with

[1] Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 26:1547-73, 2015

longer follow-up. The ESC noted that the data presented in the PSCR were not independently evaluated.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
RESORCE	A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib	Bayer Healthcare AG: Clinical Study Report: 23 September 2016 ClinicalTrials.gov identifier: NCT01774344
	Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial.	The Lancet 2017; 389 (10064):56-66.
	Erratum: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial.	The Lancet 2017; 389 (10064):36
	Bruix J, Finn RS, Kudo M, et al. RESORCE: An ongoing randomized, double-blind, phase III trial of regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing on sorafenib (SOR).	Journal of Clinical Oncology 2014; 32 (15).
	Bruix J, Merle P, Granito A, et al. Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, randomized phase 3 RESORCE trial.	Annals of Oncology 2016; 27 ii140-ii141.
	Bruix J, Merle P, Granito A, et al. Efficacy, safety, and health-related quality of life (HRQoL) of regorafenib in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, double-blind phase 3 RESORCE trial.	Annals of Oncology 2016; 27
	Cheng AL, Finn RS, Kudo M, et al. Regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing following sorafenib: An ongoing randomized, double-blind, phase III trial.	Journal of Clinical Oncology 2013; 31 (15).
	J. Bruix, P. Merle, A. Granito, et al. Survival by pattern of tumor progression during prior sorafenib (SOR) treatment in patients with hepatocellular carcinoma (HCC) in the phase III RESORCE trial comparing second-line treatment with regorafenib (REG) or placebo	Journal of Clinical Oncology 2017; 35 (4):
	R. S. Finn, P. Merle, A. Granito, et al. Outcomes with sorafenib (SOR) followed by regorafenib (REG) or placebo (PBO) for hepatocellular carcinoma (HCC): Results of the international, randomized phase 3 RESORCE trial	Journal of Clinical Oncology 2017; 35 (4):
	G. Han, S. Qin, T. Song, et al. Efficacy and safety of regorafenib (REG) versus placebo (PBO) in Chinese patients with hepatocellular carcinoma (HCC) progressing on sorafenib (SOR): Subgroup analysis of the international, randomized phase 3 RESORCE trial	Hepatology International 2017; 11 (1): S9-S10
	A. Solms, B. Ploeger, I. Reinecke, et al.Exposure-response (ER) relationship of regorafenib (REG) in patients with hepatocellular carcinoma (HCC)	Journal of Clinical Oncology 2017; 35 (4):
	A. Solms, I. Reinecke, S. Fiala-Buskies, et al. Exposure-response relationship of regorafenib efficacy in patients with hepatocellular carcinoma.	European Journal of Pharmaceutical Sciences 2017;

Source: Table 2-10, p. 39-41 of the submission.

6.5 The key features of the direct randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Regorafenib vs. BSC						
Bruix 2017	573	R, DB, MC 33 months	Low	Progressed following sorafenib.	OS, PFS	Survival and progression free gain.

Abbreviations: DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.

6.6 The trial design had a low risk of selection, performance, detection, attrition and reporting bias. The ESC noted that the submission acknowledged that hand-foot reaction is a known adverse event for tyrosine kinase inhibitors, so it was a potential unmasking factor associated with regorafenib treatment. Patients in RESORCE were permitted to continue treatment beyond progression, at the discretion of the clinical investigator.

6.7 The PBAC noted that patients included in the RESORCE trial had to meet strict eligibility criteria in terms of Child-Pugh A liver function, had tolerated sorafenib 400 mg+ daily for >20 days and did not discontinue for toxicity, ECOG PS 0-1. Patients with HIV, HBC-HCV co-infection were excluded, as were patients with large and untreated oesophageal varices due to bleeding risk. The PBAC noted that patients included in the trial had an average age of 63 years, 38% were recruited in Asia, and 66% had an ECOG PS of 0.

6.8 The PBAC noted the comparison between patients in the RESORCE trial and patients with HCC initiated for treatment with sorafenib between 2007 and 2014 in eight Australian tertiary hospitals[2]. The PBAC noted that a higher proportion of patients in Doyle et al (2016) compared to patients in the RESORCE trial had worse liver function and worse ECOG performance status. The PBAC also noted that patients in the RESORCE trial had an average treatment duration for sorafenib of 7.8 months (compared with 5.3 months in the SHARP trial, the pivotal trial for sorafenib in HCC[3]). The PBAC considered that patients recruited into the RESORCE trial are likely to be younger and fitter, tolerate systemic therapies better, and have longer survival, compared to the Australian population for the requested listing.

Comparative effectiveness

6.9 A significant increase in terms of OS, PFS and time to progression (TTP) was observed for regorafenib compared to BSC. The estimated HR=0.627 (95% CI: 0.500 - 0.785) for OS and HR=0.455 (95% CI: 0.371-0.558) for PFS, implied a 37% and 55% reduced relative risk of death and progression in the regorafenib group compared with the BSC group, respectively. The benefit of regorafenib treatment for disease control

[2] Doyle et al. 2016. Sorafenib in the treatment of hepatocellular carcinoma: a multi-centre real-world study. *Scand J Gastroenterol,* 51**,** 979-85.

[3] Llovet et al. 2008. Sorafenib in advanced hepatocellular carcinoma. *NEJM*, 359(4), 378-90.

was mainly demonstrated in the proportion of patients achieving stable disease (54.4% versus 32% in the BSC group), with an objective response occurring in only 11% of patients treated with regorafenib (versus 4% in the BSC group).

Table 4: Results of overall survival, progression free survival and time to progression in the RESORCE trial

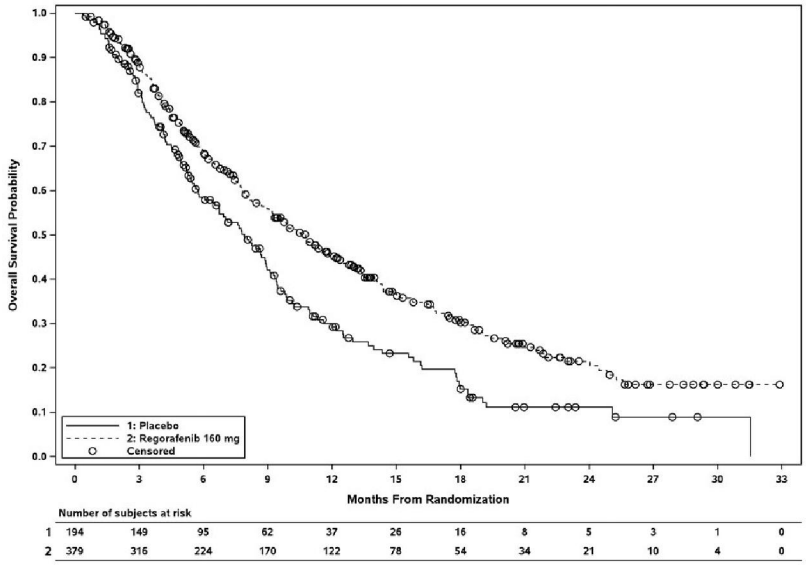
Trial ID: RESORCE	Reg n/N with event (%)	Reg Median time to event (95% CI)	BSC n/N with event (%)	BSC Median time to event (95% CI)	Difference months (95% CI)	P value (log rank test)	HR (95% CI)
OS	233/379 (61.5%)	10.6 (9.1–12.1)	140/194 (72.2%)	7.8 (6.3–8.8)	2.8 (2.8 – 3.3)	< 0.0001	**0.627 (0.500 - 0.785)**
PFS	293/379 (77.3%)	3.1 (2.8–4.2)	181/194 (93.3%)	1.5 (1.4–1.6)	1.6 (0 – 2.6)	< 0.0001	**0.455 (0.371 - 0.558)**
TTP	274/379 (72.3%)	3.2 (2.9–4.2)	173/194 (89.2%)	1.5 (1.4–1.6)	1.7 (0.1 – 0.9)	< 0.00001	**0.442 (0.358 - 0.545)**

Abbreviations: BSC= Best supportive care; CI = confidence interval; HR = Hazard ratio; OS= overall survival; PFS= progression free survival; TTP= time to progression.
Source: Table 2-25 to 2-27, p. 70 to 74 of the submission.
Note: Bold text indicates a statistically significant value.

6.10 The ESC noted that although not independently evaluated, the data presented in the PSCR demonstrated that the gain in OS was maintained with longer follow-up.

6.11 The Kaplan-Meier data are presented in Figure 1. The gain in median OS was 2.8 months.

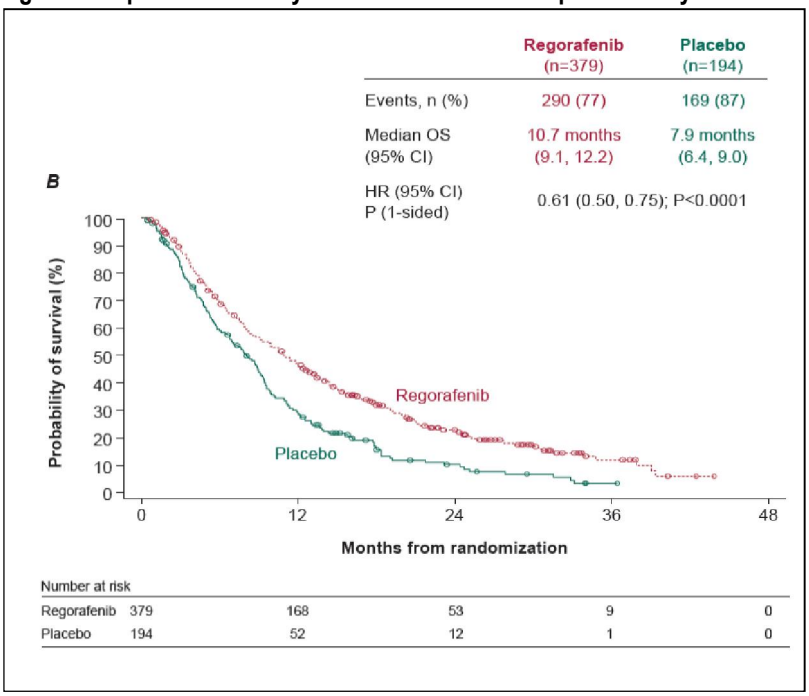
Figure 1. Kaplan Meier curve for overall survival (Full Analysis Set)



Source: Figure 2-6, P. 71 of the submission

6.12 The Kaplan-Meier data from the updated analysis provided in the PSCR are presented in Figure 2.

Figure 2: Kaplan–Meier analysis of overall survival - updated analysis



Source: PSCR (p4, Attachment A)

6.13 The results from the RESORCE trial showed that there were no statistically significant differences in quality of life (QoL) between regorafenib and BSC, despite improved PFS. On average, worse QoL values were observed for regorafenib compared with BSC for all QoL questionnaires. These were statistically significantly worse for the FACT-HEP and Trial Outcomes Index, but did not achieve the minimally important differences for those questionnaires. These worse QoL average values for regorafenib could be explained by the increased toxicity associated with regorafenib. A summary of key QoL outcomes is presented in Table 5.

Table 5: Results for patient reported outcomes (HRQoL) in the RESORCE trial

LSM time-adjusted AUC (95% CI)	Reg	BSC	Difference	P value	MID
EQ-5D 3L index	0.76 (0.75-0.78)	0.77 (0.75-0.79)	-0.01 (-0.03-0.02)	0.4695	0.1
EQ-5D VAS	71.68 (70.46-72.90)	73.45 (71.84-75.06)	-1.77 (-3.58-0.04)	0.0558	10
FACT-General	75.14 (74.12-76.16)	76.55 (75.20-77.90)	-1.41 (-2.93-0.11)	0.0698	6-7
FACT-Hep total	129.31 (127.84-130.79)	133.17 (131.21-135.12)	**-3.85** (-6.06 - -1.65)	0.0006	8-9
Trial outcome index	91.47 (90.30-92.64)	95.52 (93.98-97.07)	**-4.05** (-5.79 - -2.31)	<0.0001	7-8

Abbreviations: AUC= area under the curve; CI= confidence intervals; FACT= Functional assessment cancer therapy; LSM= least squares mean; MID= minimally important difference; VAS= visual analogue scale.
Source: Online Table 12, p.19 of the RESORCE supplementary appendix.
Note: Bold text indicates a statistically significant value.

Comparative harms

6.14 Safety data presented in the submission were obtained from the RESORCE trial and are summarised in Tables 6 and 7. There is a boxed warning included in the Product Information (PI) for hepatotoxicity associated with regorafenib. The rates of liver-related adverse events and liver failure with regorafenib in the RESORCE trial were not higher when compared with other regorafenib trials (for different indications). The TGA Delegate's Overview stated "There is currently insufficient data to assess whether patients with underlying hepatic impairment as a result of HCC, are likely to experience more severe hepatotoxicity if treated with regorafenib. Use in this subset of patients should be closely monitored".

6.15 Patients treated with regorafenib were 3 times more likely to suffer any grade 3 or 4 drug-related adverse event compared to BSC (Table 6). The data from the RESORCE trial showed that more patients treated with regorafenib (31.6%) reported infections and infestations than patients treated with BSC (17.2%). This was acknowledged by the TGA and a precautionary warning was included in the PI.

6.16 The ESC noted that hand-foot skin reaction (HFSR) or Palmar-Plantar erythrodysesthesia, which causes redness, swelling, blistering and pain on the palms of the hands and/or the soles of the feet, occurred with grade 3 severity in 12.3% of patients in the regorafenib arm, compared with 0.5% in the BSC arm. Although the submission acknowledged that HFSR was a known side-effect of tyrosine kinase inhibitors, the ESC considered that it was likely to cause significant detriment to a patient's QoL.

6.17 In addition to the grade 3 or 4 AEs and HFSR experienced by patients treated with regorafenib, the PBAC noted that there were a number of grade 5 AEs for patients treated in the RESORCE trial including myocardial infarction, upper GI haemorrhage, intracranial haemorrhage, hepatic failure, encephalopathy and gastric perforation. The PBAC considered that the risk of bleeding events may be higher in the Australian population, as patients with bleeding risk were excluded from the RESORCE trial.

6.18 The PBAC noted that there was also a substantial increase in bothersome grade 1 and 2 AEs including hand-foot syndrome, diarrhoea, fatigue, hypertension, anorexia and abdominal pain for patients treated with regorafenib, that are likely to impact on patient quality of life as regorafenib is a chronic oral therapy.

6.19 Overall, the PBAC considered that regorafenib was associated with substantial toxicity which may be worse in the Australian population under the proposed listing.

Table 6: Summary of key adverse events in the RESORCE trial.

	Regorafenib N = 374 (100%)	BSC N = 193 (100%)	Relative risk (95% CI)	Risk difference (95% CI)
Any drug-related AE	**346 (92.5%)**	**100 (51.8%)**	**1.79 (1.55, 2.05)**	**0.41 (0.33, 0.48)**
Worst CTCAE grade:				
Grade 3	173 (46.3%)	31 (16.1%)	**2.88 (2.05, 4.05)**	**0.30 (0.23, 0.37)**
Grade 4	14 (3.7%)	1 (0.5%)	7.22 (0.96, 54.53)	**0.03 (0.01, 0.05)**
Grade 5 (death)	7 (1.9%)	2 (1.0%)	1.81 (0.38, 8.61)	0.01 (-0.01, 0.03)
Grade 3 or 4	187 (50.0%)	32 (16.6%)	**3.02 (2.16, 4.20)**	**0.33 (0.26, 0.41)**
Grade 3, 4 or 5	194 (51.9%)	34 (17.6%)	**2.99 (2.17, 4.12)**	**0.35 (0.28, 0.42)**
Serious	39 (10.4%)	5 (2.6%)	**4.03 (1.61, 10.05)**	**0.08 (0.04, 0.12)**
Leading to dose modification	202 (54.0%)	20 (10.4%)	**5.21 (3.41, 7.97)**	**0.44 (0.37, 0.50)**
Leading to permanent discontinuation of study drug	39 (10.4%)	7 (3.6%)	2.58 (0.57, 11.66)	0.02 (-0.01, 0.04)

Abbreviations: AE= adverse event; BSC= best supportive care; CI = confidence interval; CTCAE= Common Terminology Criteria for Adverse Events; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk
Source: Table 2-32, p. 83 of the submission.
Note: Bold text indicates a statistically significant value.

Table 7: Summary of key drug-related TEAEs in the RESORCE trial (more than 5% in either treatment group).

CTCAE drug related TEAEs	Regorafenib N=374 (100%)			BSC N=193 (100%)			Relative risk (95% CI)	Risk difference (95% CI)
	Grade 3	Grade 4	Total (Grade 3+4)	Grade 3	Grade 4	Total (Grade 3+4)	Total (Grade 3+4)	Total (Grade 3+4)
Hypertension	48 (12.8%)	0	48 (12.8%)	6 (3.1%)	0	6 (3.1%)	**4.13 (1.80, 9.47)**	**0.10 (0.06, 0.14)**
HFSR	46 (12.3%)	0	46 (12.3%)	1 (0.5%)	0	1 (0.5%)	**23.74 (3.30, 170.82)**	**0.12 (0.08, 0.15)**
Blood bilirubin increased	19 (5.1%)	0	19 (5.1%)	2 (1.0%)	0	2 (1.0%)	**4.90 (1.15, 20.83)**	**0.04 (0.01, 0.07)**
AST increased	17 (4.5%)	3 (0.8%)	20 (5.3%)	9 (4.7%)	1 (0.5%)	10 (5.2%)	1.03 (0.49, 2.16)	0.00 (-0.04, 0.04)

Abbreviations: BSC= best supportive care; CI = confidence interval; HFSR= hand–foot skin reaction; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; TEAE= treatment-emergent adverse events.
Source: Table 2-33, p. 85 of the submission.
Note: Bold text indicates a statistically significant value.

Benefits/harms

6.20 A summary of the comparative benefits and harms for regorafenib versus BSC is presented in the table below.

Table 8: Summary of comparative benefits and harms for regorafenib and best supportive care (BSC)

Time-to-event outcome OS: RESORCE trial				
	Regorafenib	**BSC**	**Absolute difference**	**HR (95% CI)**
Survival* n/N (%)	233/379 (61.5)	140/194 (72.2)	10.7%	**0.63 (0.50, 0.79)**
Median (months)	10.6 (9.1, 12.1)	7.8 (6.3, 8.8)	2.8	-
Time-to-event outcome PFS: RESORCE trial				
Progressed* n/N (%)	293/379 (77.3)	181/194 (93.3)	16%	**0.46 (0.37, 0.56)**
Median (months)	3.1 (2.8, 4.2)	1.5 (1.4, 1.6)	1.6	-

Progressed* n/N (%)						
RESORCE trial	**Regorafenib n/N**	**BSC n/N**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Regorafenib	**BSC**	
Hypertension[a]	49/374	15/193	**4.13 (1.80, 9.47)**	13.1	7.8	**0.10 (0.06, 0.14)**
HFSR[a]	46/374	1/193	**23.74 (3.30, 170.82)**	12.6	<1	**0.12 (0.08, 0.15)**
Blood bilirubin increased[a]	25/374	4/193	**4.90 (1.15, 20.83)**	6.7	2.1	**0.04 (0.01, 0.07)**
AST increased[a]	19/374	10/193	1.03 (0.49, 2.16)	5.1	5.2	0.00 (-0.04, 0.04)

Notes: * Median duration of follow-up OS: RESORCE Trial = 7 months, Maximum duration of follow-up OS: RESORCE Trial = 33 months.
[a] Only grade 3 and 4 adverse events are reported.
Note Grade 3 HFSR defined as Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living
Abbreviations: AST= aspartate aminotransferase; BSC= best supportive care; HFSR= Hand–foot skin reaction; HR = hazard ratio; RD = risk difference; RR = risk ratio
Source Table 2-25 to 2-27, p. 70 to 74 and Table 2-33, p. 85 of the submission.
Note: Bold text indicates a statistically significant value.

6.21 On the basis of the direct evidence presented by the submission, for every 100 patients treated with regorafenib in comparison to BSC and followed over the entire trial duration of 33 months:

- Approximately 11 more patients will survive, with a median increase in survival of 2.8 months.
- Approximately 16 more patients will remain progression free, with a median increase in progression free survival of 1.8 months.
- Approximately 10 more patients will experience severe hypertension.
- Approximately 12 more patients will experience a severe hand-foot skin reaction with moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

Clinical claim

6.22 The submission claimed that regorafenib was superior to BSC for the treatment of advanced HCC, providing a statistically significant increase in OS, but was associated, "with a [slightly] higher incidence of drug related adverse events which were well tolerated and did not significantly impact patient QoL". While the clinical claim was

supported by the statistical significance of the data presented with respect to OS, the clinical significance and patient relevance of the magnitude of benefit (2.8 months median survival) was unclear in the context of patients with advanced HCC, particularly in the light of the detrimental effect of treatment related adverse events on patient QoL.

- Acknowledging the significantly higher incidences of AEs in the regorafenib arm, the PSCR removed the word 'slightly' from the clinical claim. The ESC noted that this implicitly changed the clinical claim to one of superior efficacy and inferior safety, compared with BSC.
- The PSCR maintained that the potential for increased toxicity did not have a significant clinical impact on patient reported outcomes. The pre-PBAC response maintained this position, arguing that because the differences in QoL values did not achieve minimally important differences, the impact of these grade 3/4 AEs is not clinically meaningful.
- The ESC considered that the modest improvement in OS was likely to be clinically meaningful, but advised that this benefit should be weighed against the significant impact of treatment related AEs.
- The pre-PBAC claimed that most AEs occurred early in the course of treatment and were managed with dose modification or reductions, while cutaneous AEs (including HSFR) are dose dependent and may be correlated with treatment effect and better efficacy outcomes.

6.23 The ESC noted that the RESORCE trial excluded patients who tested positive for human immunodeficiency virus (HIV), co-infected with hepatitis B/hepatitis C virus (HBV/HCV) (common cause of HCC). As this was not included as a criterion in the proposed PBS restriction, the ESC advised that the impact of this disparity between the trial population and the proposed PBS population on the efficacy, safety and cost-effectiveness of regorafenib, was unclear.

6.24 The PBAC considered that the claim of superior comparative effectiveness was reasonable based on modest improvements in OS, PFS and time to progression.

6.25 The PBAC considered that the claim of inferior safety was reasonable. However the PBAC considered that the evidence presented in the submission did not support the submission's claim of no significant impact of regorafenib toxicity on QoL. Regorafenib patients are 3 times more likely to suffer any grade 3 or 4 adverse event compared to BSC. In addition, the trial reported numerically lower average QoL for regorafenib compared with BSC, which may reflect the increased toxicity.

Economic analysis

6.26 The economic evaluations presented were a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). Health benefits were reported as life years gained (LYGs) and quality adjusted life years (QALYs) gained, respectively.

Table 9: Key components of the economic evaluation

Component	Description
Perspective	Health care perspective
Type of analysis	CEA and CUA
Outcomes	LYGs and QALYs
Time horizon	5 years in the base case vs 2.77 years (33 months) in the RESORCE trial.
Methods used to generate results	Partitioned survival model
Health states	Progression Free (PFS), Progressive Disease (PD) and Dead.
Cycle length	28 days
Discounting	5% per year for costs and benefits
Area under the curve (AUC)	The KM estimates for PFS and OS were derived directly from the RESORCE trial.
Software package	Microsoft Excel 2016

Abbreviations: AUC= area under the curve; BSC= best supportive care; KM= Kaplan-Meier; LYG= life years gained; N/A= not applicable; OS= overall survival; PD= progressive disease; PFS= progression free survival; QALYs= quality adjusted life years.
Source: Table 3-1, p. 105 of the submission.

6.27 A summary of the key drivers of the model are shown in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Application of extrapolation	Extrapolation was only conducted for regorafenib, not BSC. The model assumed that the treatment effect continued beyond median follow-up of 7 months for up to 5 years.	High, favoured regorafenib
Time point for extrapolation	The model extrapolated from month 33 onwards for regorafenib only. This time point was inappropriate due to the small numbers of patients at risk. By extrapolating from month 33 in the regorafenib arm, the submission relied on highly uncertain data where there were no patients at risk.	High, favoured regorafenib
Time horizon	Applying extrapolations for regorafenib only over a 5-year time horizon resulted in a 34% reduction in the ICER when comparing it to the trial duration period (33 months).	High, favoured regorafenib. The ESC considered that while a five-year time horizon may be appropriate in this patient population, it was inappropriate to have not extrapolated the BSC arm over that time horizon.
Utilities	The model used average utility per health state. These assumed patients had an equivalent quality of life independent of whether they were receiving regorafenib or BSC. This contrasts with the findings of the trial where the utility values were, on average, lower but not statistically different for regorafenib patients compared to BSC.	Moderate, favoured regorafenib

Source: Table 3-25, p. 177 of the submission.
Abbreviations: BSC= best supportive care; ICER= incremental cost effectiveness ratio

6.28 In contrast with the proposed restriction, patients in the trial could continue receiving treatment after progression was established if, in the opinion of the investigator, the treatment was still providing clinical benefit. The ESC noted that the survival advantage for regorafenib observed in the RESORCE trial may thus capture

use beyond progression and may therefore exceed what might be expected in clinical practice in Australia. The pre-PBAC response indicated that in the RESORCE trial 37% of patients continued treatment for 7 days or more beyond radiological progression (40% in the placebo arm and 35% in the regorafenib arm). The sponsor suggested that this would be consistent with current Australian clinical practice where some patients continue treatment until clinical progression (ECOG ≥3) or symptomatic progression.

6.29 The submission claimed that the extrapolation for PFS was supported by the data which showed 3% of patients were free of disease progression at the end of study follow-up. The submission relied on data that were highly uncertain; no patients were at risk at month 27.

6.30 Only costs and outcomes in the regorafenib arm were extrapolated to five years. No extrapolations were applied to BSC. This is likely to have biased the results in favour of regorafenib.

6.31 The economic model presented in the submission did not contain sufficient data to allow the BSC data to be extrapolated in the same manner as the regorafenib arm, rendering the sensitivity analyses provided around the regorafenib only arm of limited value to the overall assessment of cost-effectiveness.

- The PSCR argued that since a reasonable number of patients were still free of progression (3%) and alive (16%) in the regorafenib group (versus no patients in BSC group) at the end of the trial follow-up period, the base case economic model only considered the results of the regorafenib treatment arm extrapolated to the time horizon of 5 years.
- However, the ESC noted that the updated Kaplan-Meier curves provided in the PSCR indicated that at 30 months, 9% of the patients in the BSC arm were still alive. The ESC therefore considered that it was inappropriate for the submission to have extrapolated the regorafenib arm alone.
- The PBAC noted that the pre-PBAC response provided univariate and multivariate sensitivity analyses that extrapolated both the regorafenib and BSC arms. The PBAC agreed with ESC that outcomes and costs for both arms should be extrapolated.

6.32 For OS, a Gompertz distribution was fitted from day 112 (cycle 4) onwards in the base case. Thus, the data used to inform the extrapolation function excluded the first 112 days of the observed data. No other testing, other than visual inspection, was used to justify the point for extrapolation. This was potentially significant given that the median follow-up in the trial was only 7 months. In a sensitivity analysis, the submission applied a dependant model to the extrapolation of all the available data for the regorafenib arm, and assuming a Gompertz distribution, resulting in an increased ICER from a base case of $45,000/QALY - $75,000/QALY.

- The PSCR disagreed that the choice of inflection point for the base case was inappropriate due to the median follow-up duration of 7 months, noting that a 56-day inflection point (i.e. excluding the first 56 days of data in informing the extrapolation) had a minimal impact on the ICER.
- The ESC noted the PSCR's arguments, but considered that the means of choosing the inflection point remained arbitrary, given that an adequately strong justification for not using all observed data to inform the extrapolation was not provided.
- The PBAC agreed with ESC that the piecewise extrapolation with the Gompertz function was inappropriate and noted that sensitivity analyses were provided in the pre-PBAC which did not use this approach.

6.33 Use of the Weibull instead of the Gompertz function for extrapolation of the regorafenib OS data had a minimal impact on the ICER (increasing by 5.5%). In the absence of extrapolation for the BSC arm, there was considerable uncertainty associated with these ratios, despite the minimal impact observed from changing the form of the extrapolation function applied.

6.34 The submission applied its extrapolation of the regorafenib OS and PFS data from month 33 onwards.

- The ESC noted that submission thus relied on highly uncertain data as the Kaplan-Meier plots for both OS and PFS were driven by a small number of at-risk patients at 33 months. The extremely low number of patients at risk observed in the last months of the trial follow up period could be attributed to the relatively immature follow-up or the short survival expected for these patients given the severity of the disease.
- The PSCR argued that the survival data presented were mature and that the 7 month median follow-up is driven by the fact that the trial reached the pre-specified number of events for reporting the primary analysis as defined in the trial's statistical analysis protocol (SAP). The PSCR further argued that the pattern and distribution of censoring was more relevant than the extent of censoring.
- The ESC disagreed with the PSCR, and advised that irrespective of the pattern, distribution or extent of censoring, extrapolating from month 33 was inappropriate, due to the substantial uncertainty introduced by the very sparse number of events recorded by the time the survival curves reached this time point.
- The PBAC noted that the pre-PBAC response provided sensitivity analyses extrapolating PFS and OS from the last observation and from the median follow-up. The PBAC considered that extrapolation from the median follow-up was the more appropriate approach.

6.35 The ESC noted that the submission proposed a 5-year time horizon. The ESC further noted that the ICER was increased by 34% when no extrapolation occurred, i.e. the trial duration period (33 months), was considered. The ESC advised that while the proposed time horizon of 5 years was likely to be reasonable, the impact on the ICER was compounded by (i) extrapolating the regorafenib arm alone; (ii) arbitrary choice in the point of inflection in informing the extrapolation and (iii) extrapolating from a time point (33 months) where a sparse number of patients remained in the trial.

6.36 A stepped economic evaluation was presented (see Table 11). Step 1 was a trial-based economic evaluation with only the costs of primary treatment (medicines) considered. Step 2 extrapolated results to a 5-year time horizon. No extrapolation was conducted for the BSC arm. Step 3 in the submission included all resource use in addition to the drug price. Finally, Step 4 transformed the outcome, LYG, to QALYs.

Table 11: Results of the stepped economic evaluation

Step	Cost			Outcomes			ICER
	Reg	BSC	Inc	Reg	BSC	Inc	
Step 1. RESORCE trial (time horizon 33 months)	$[redacted]	$0	$[redacted]	1.11	0.81	0.30	$[redacted]/LYG
Step 2. RESORCE trial extrapolated to 5 years	$[redacted]	$0	$[redacted]	1.26	0.81	0.45	$[redacted]/LYG
Step 3. RESORCE trial extrapolated to 5 years including all resource use	$[redacted]	$3,508	$[redacted]	1.26	0.81	0.45	$[redacted]/LYG
Step 4. RESORCE trial extrapolated to 5 years including all resource use and transformed to QALY's	$[redacted]	$3,508	$[redacted]	0.93	0.60	0.34	$[redacted]/QALY

Abbreviations: ICER= incremental cost effectiveness ratio; Inc= incremental; LYG= life years gained; QALYs= quality adjusted life years; Reg= regorafenib
Source: Table 3-24, p. 175 of the submission.

The redacted table shows ICERs in the range of $45,000 - $75,000 per LY or QALY gained.

6.37 The model reported QALYs as the final health outcome by using average utility per health state. These assumed patients had an equivalent quality of life independent of whether they were receiving regorafenib or BSC. This contrasts with the findings of the trial where the utility values were, on average, lower for regorafenib patients compared to BSC (although this difference was not statistically significant).

- The PSCR maintained that utility values in RESORCE trial did not show any clinically meaningful or statistical significant differences between the treatment groups.
- The ESC considered that the approach of using same utility value for both treatment groups was optimistic given the utility scores favoured BSC (albeit not statistically significantly).

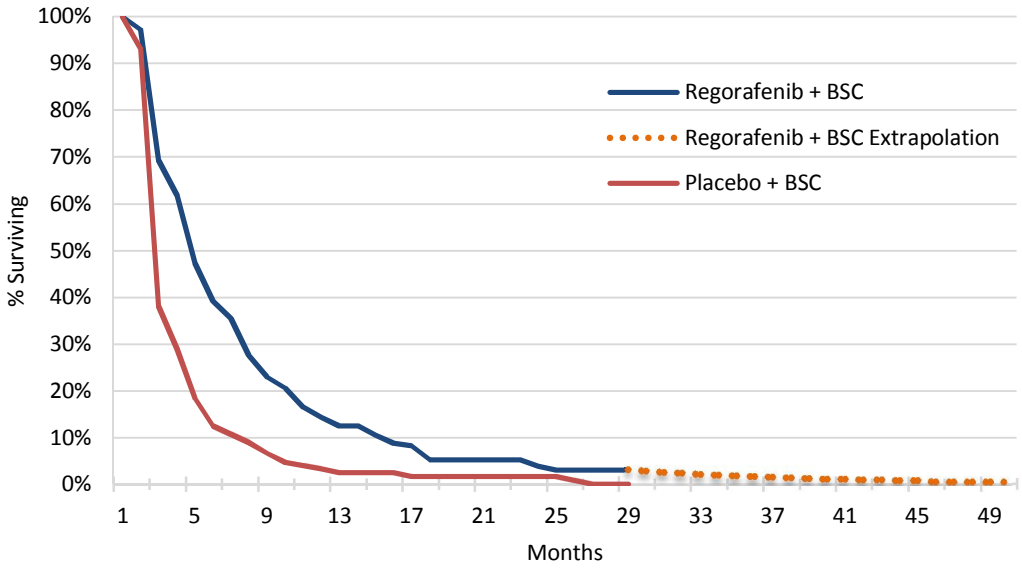
- The PSCR also noted that in order to take into consideration the negative impact from the regorafenib toxicity, disutility values due to drug related TEAEs ≥ Grade 3 were applied to the proportion of patients experiencing the corresponding TEAEs in each health state.
- The PBAC agreed with ESC that the utility values should be based on the RESORCE trial values, rather than using an average utility per health state. The PBAC noted that the pre-PBAC response provided sensitivity analyses applying trial-based utilities.

6.38 The transformation of the outcome from LYG to QALYs had an important impact on the cost-effectiveness results. The ESC noted that the respective ICERs were $15,000/LYG - $45,000/LYG, and $45,000/QALY - $75,000/QALY (i.e. 25% higher after adjusting for QoL). Using a trial-based time horizon and transforming the outcomes to QALYs resulted in a further increase in the ICER from$45,000/QALY - $75,000/QALY to $75,000/QALY - $105,000/QALY.

6.39 The submission applied appropriate methodology to estimate the total expected costs. The sources for valuing health resources and the cost of hospital admissions due to TEAEs were reasonable.

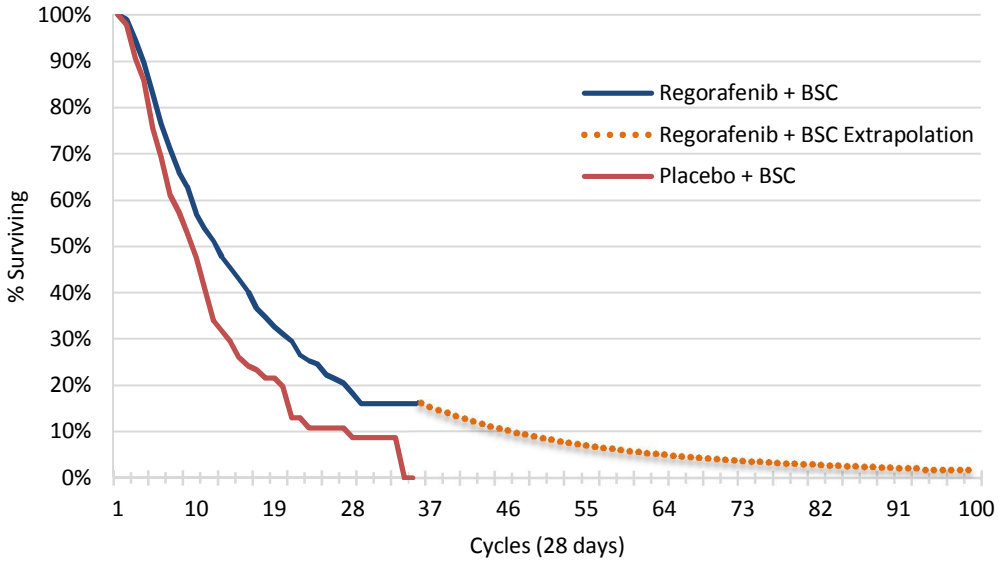
6.40 The modelled results for PFS and OS and the source Kaplan-Meier estimates are presented in Figure 3 and 4. The comparison of the KM component of the OS curve to the extrapolated period shows that a substantial part of the benefit estimated for regorafenib comes from the extrapolated data.

Figure 3: Kaplan-Meier and extrapolated values: progression free survival



Source: Figure 3-16, p. 166 of the submission.

Figure 4: Kaplan-Meier and extrapolated values: overall survival



Source: Figure 3-17, p.167 of the submission.

6.41 Selected univariate sensitivity analyses specified by the submission and additional analyses conducted during the evaluation are presented in Table 12.

Table 12: Results of sensitivity analyses

	Cost	Outcomes	ICER ($/QALY)
	Incremental Reg vs BSC	Incremental Reg vs BSC	
Base case			
Base case	$[redacted]	0.34	$[redacted]
One Way Sensitivity analysis			
OS – Log-logistic extrapolation for regorafenib only	$[redacted]	0.37	$[redacted]
OS – Weibull extrapolation for regorafenib only	$[redacted]	0.32	$[redacted]
OS – Log-Normal extrapolation for regorafenib only	$[redacted]	0.37	$[redacted]
OS – Exponential extrapolation for regorafenib only	$[redacted]	0.31	$[redacted]
OS – Gamma extrapolation for regorafenib only	$[redacted]	0.31	$[redacted]
OS – Piecewise Cycle 3 (56 days) extrapolation for regorafenib only	$[redacted]	0.34	$[redacted]
OS – No Piecewise Gompertz extrapolation for regorafenib only	$[redacted]	0.29	$[redacted]
Utility (PFS: 0.76; PD: 0.68)	$[redacted]	0.32	$[redacted]
Utility (AE Literature)	$[redacted]	0.33	$[redacted]
Time horizon 3 years	$[redacted]	0.24	$[redacted]
Time horizon 4 years	$[redacted]	0.30	$[redacted]
Discount rate: 0%	$[redacted]	0.37	$[redacted]
Discount rate: 3.5%	$[redacted]	0.35	$[redacted]
Additional sensitivity analysis			
No PFS extrapolation applied to base case (Step 4)	$[redacted]	0.334	$[redacted]
Extrapolation for OS from month 12 to year 5 applied to base case (Step 4)	$[redacted]	0.310	$[redacted]
Clinical trial time horizon (33 months) and outcome converted to QALYs (Step 1)*	$[redacted]	0.215	$[redacted]

Abbreviations: AE= adverse event; BSC= best supportive care; ICER= incremental cost effectiveness ratio; OS= overall survival; PD= progressive disease; PFS= progression free survival; QALYs= quality adjusted life years; Reg= regorafenib; SPA= special price agreement; TEAEs= treatment emergent adverse event.
Note: * The submission had applied an extrapolation to PFS in estimating the within trial analysis. This has been removed in this sensitivity analysis, hence the difference in incremental cost from the submission's Step 1.
Source: Table -27, p. 180 of the submission.

The redacted table shows ICERs in the range of $45,000/QALY - $105,000/QALY.

6.42 The results from the sensitivity analyses provided in the submission, showed that the ICER estimates were most sensitive to variations in the time horizon (3 and 4 years) and structural uncertainty by modelling OS through a survival dependent model (not a piecewise). These analyses were applied to a model in which only the regorafenib arm alone had been extrapolated, therefore the impact of applying extrapolations to the BSC arm remained uncertain.

6.43 The ESC advised that additional univariate analyses and multivariate analyses testing the following assumptions would be informative:

- extrapolating both regorafenib and BSC arms;
- applying extrapolations from different time points, including from the point of median follow-up;
- using all observed survival data (i.e. from day 1) to inform the parametric function used to undertake the extrapolations; and
- applying trial-based utility values.

6.44 The ESC considered that while using the updated Kaplan-Meier curves provided in the PSCR in the extrapolation of both arms would potentially be more informative, any revised extrapolation conducted with updated data would not be independently evaluated in time for PBAC's consideration at its March 2018 meeting.

6.45 The PBAC noted the base case ICER presented was $15,000 - $45,000 per additional life year and $45,000 - $75,000 per QALY gained. The PBAC considered that this base case is likely to underestimate the ICER due to the above issues identified in the commentary and raised by ESC. The Committee noted that univariate and multivariate sensitivity analyses were presented in the pre-PBAC response as requested (Table 13). These analyses were based on the original Kaplan-Meier curves in the submission. The PBAC noted that the multivariate sensitivity analysis as specified by ESC, where OS and PFS are extrapolated from the median follow-up for both regorafenib and BSC arms, no piecewise Gompertz model for OS and using trial-based utilities gave an ICER of $75,000 - $105,000 per QALY gained. The PBAC considered this revised analysis was the most appropriate base case for informing the ICER.

6.46 In view of the revised analyses the sponsor reduced the requested AEMP for regorafenib by approximately [redacted]% from $[redacted] to $[redacted] per bottle of 28 tablets. The revised proposed price for regorafenib reduced the ICER from $75,000 - $105,000 per QALY gained, to $45,000 - $75,000 per QALY gained.

6.47 The pre-PBAC response argued that the revised price gives an ICER of $45,000 - $75,000 per QALY gained with extrapolation from the median follow-up for both groups, which compared favourably with the ICER for sorafenib in HCC from 2008. The PBAC noted differences between second line therapy with regorafenib and first line treatment with sorafenib for unresectable HCC, and considered that the toxicity of regorafenib and concern that the benefit observed in the trial in relatively fit patients may not be realised in clinical practice were also relevant factors.

Table 13: Additional univariate and multivariate analyses

	Submission			Revised price		
	Incr. Cost	Incr. QALYs	ICER ($/QALY)	Incr. Cost	Incr. QALYs	ICER ($/QALY)
Submission	$[redacted]	0.34	$[redacted]	$[redacted]	0.34	$[redacted]
Univariate sensitivity analyses						
OS Extrapolation incl. BSC: Last observation	$[redacted]	0.27	$[redacted]	$[redacted]	0.27	$[redacted]
OS Extrapolation incl. BSC: Median	$[redacted]	0.25	$[redacted]	$[redacted]	0.25	$[redacted]
OS Extrapolation incl. BSC: Last observation, No piecewise Gompertz	$[redacted]	0.25	$[redacted]	$[redacted]	0.25	$[redacted]
PFS Extrapolation incl. BSC: Last observation	$[redacted]	0.34	$[redacted]	$[redacted]	0.34	$[redacted]
PFS Extrapolation incl. BSC: Median	$[redacted]	0.33	$[redacted]	$[redacted]	0.33	$[redacted]
Utilities: regorafenib (PFS: 0.776 PD: 0.738) and BSC (PFS: 0.783 PD: 0.741)	$[redacted]	0.33	$[redacted]	$[redacted]	0.33	$[redacted]
Multivariate sensitivity analyses						
OS and PFS Extrapolation incl. BSC : Median	$[redacted]	0.25	$[redacted]	$[redacted]	0.25	$[redacted]
OS Extrapolation incl. BSC: Median, No piecewise Gompertz	$[redacted]	0.21	$[redacted]	$[redacted]	0.21	$[redacted]
OS and PFS Extrapolation incl. BSC: Median, No piecewise Gompertz for OS	$[redacted]	0.21	$[redacted]	$[redacted]	0.21	$[redacted]
OS and PFS extrapolation incl. BSC: Median, No piecewise Gompertz for OS and Utilities: regorafenib (PFS: 0.776 PD: 0.738) and BSC (PFS: 0.783 PD: 0.741)	$[redacted]	0.20	$[redacted]	$[redacted]	0.20	$[redacted]

Source: Regrorafenib pre-PBAC response, Table 2
The redacted table shows ICERs in the range of $45,000/QALY - $105,000/QALY.

Drug cost/patient/course: $22,214

6.48 The estimated average daily dose for regorafenib was estimated at 102 mg (including time off drug and treatment interruptions). The submission estimated the cost per patient/year assuming 12 months of treatment which resulted in an annual cost of $[redacted]. This implies 8.3 packs per patient/year which is higher than that estimated from data from the RESORCE trial (5.41 packs) which used the total milligrams and total treatment days per year. Based on the estimated treatment exposure (5.41 packs) from the RESORCE trial, the expected cost per patient course was $[redacted]. The PSCR acknowledged this error and reported a new cost per patient year of $[redacted]. The ESC considered that this value was an accurate estimate, and noted that the minor difference was due to the rounding in the number of packs applied.

6.49 The PBAC noted that the pre-PBAC response proposed a lower DPMQ that would reduce the cost of regorafenib per patient per course.

Estimated PBS usage & financial implications

6.50 This submission was not considered by DUSC.

6.51 The predicted use of regorafenib was estimated using an epidemiological approach. The submission used an analysis based on the 10% Medicare sample to estimate the rate of regorafenib uptake after sorafenib progression for the six years following listing.

6.52 Since the nominated comparator for this condition was BSC, there are no PBS-listed medicines substituted by the proposed medicine, noting that administration of BSC needs to be maintained while on regorafenib treatment.

6.53 Overall, a listing for regorafenib is expected to result in an incremental cost to the PBS/RPBS of less than $10 million in 2023 (Year 6). The total financial implications to the PBS and the government health budget over 6 years of subsidising regorafenib would be $30 - $60 million. The PBAC noted that the pre-PBAC response proposed a lower DPMQ that would reduce the total financial implications to the PBS and the government health budget.

Table 13: Estimated use and financial implications

	6-year time horizon considering SPA					
	2018	**2019**	**2020**	**2021**	**2022**	**2023**
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of regorafenib						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS/DHS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to State and Territory Governments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Overall net cost to Government Health Budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Note: [a]Assuming 5.41 packs per year as estimated by the submission.
Abbreviation: SPA= special price agreement.
Source: Table 4-15, p. 202 of the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.54 A 100% PBS sample of patients receiving sorafenib was available for analysis during the evaluation. The estimated number of patients was similar in the early years (2010-2013) to those presented in the submission (based on 10% PBS sample). A difference was observed in later years where use reported for sorafenib in the 100% PBS sample from 2015 to 2016 was lower than that from the 10% sample.

6.55 This difference in estimates resulted in a difference in forecasts, and potentially an overestimate in the eligible patient pool for regorafenib. The impact of applying the data from the 100% PBS sample was a reduction in the estimated eligible patient pool, and a corresponding reduction of 45% ($[redacted]) in the cost to government over six years compared to the base case results presented in the submission. Similar

variations in the financial implications were produced by varying the assumed up take rate (from 100% in the base case to 50%), and the proportion of eligible patients (from 70% in the base case to 50%). The PBAC considered that the uptake rates in the financial estimates are likely to be overestimated. The ESC noted that sensitivity analyses provided in the commentary and the PSCR demonstrated that the net cost to government is unlikely to exceed $10 million in any of the first 6 years of listing. The PBAC agreed with ESC that the overall budget impact of listing regorafenib is likely to be relatively low.

6.56 The proposed restriction is for use in patients with ECOG ≤1 (in accordance with the RESORCE trial). However, the estimates presented in the submission allow for a proportion of patients with worse performance status to access treatment with regorafenib. The ESC considered that the cost-effectiveness of regorafenib in patients with ECOG > 1 may be lower than assessed in the submission as these patients were not included in RESORCE and were potentially more susceptible to adverse events.

6.57 Similarly, the submission assumed that drug use on the PBS would mirror that in RESORCE, where patients could be treated beyond progression if there was clinical benefit. This may overestimate the use of regorafenib on the PBS, given the proposed restriction to limit use on the PBS to those who are free from disease progression.

6.58 The PBAC noted that treatment related costs for medical visits, pathology, diagnostics and AEs were included in the economic model but no costs to the MBS were included in the financial estimates. The PBAC advised that costs to the MBS should be included in the financial estimates.

Quality Use of Medicines (QUM)

6.59 The most common and/or important adverse events in the RESORCE trial were hypertension, hand–foot skin reaction (HFSR), fatigue, and diarrhoea. Although common, most were manageable by dose modification. Detailed advice, warnings and recommendations are provided in the draft Product Information. The submission presented a QUM plan focused on the management of HFSR directed to patients and training sessions for nurses and physicians.

6.60 The ESC noted that drug interactions occur with regorafenib and commonly used drugs. For example, co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). The ESC therefore advised that should regorafenib be recommended for listing, these QUM issues will require education and monitoring in clinical practice.

Financial Management – Risk Sharing Arrangements

6.61 No risk-sharing arrangements were proposed for the listing of regorafenib for use in unresectable HCC.

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

7 PBAC Outcome

7.1 The PBAC did not recommend regorafenib for patients with unresectable hepatocellular carcinoma who progressed following treatment with sorafenib on the basis of a high and uncertain incremental cost-effectiveness ratio. The PBAC considered that the toxicity associated with regorafenib was substantial, with a range of adverse events associated with regorafenib, which may be more frequent and severe in the proposed Australian population compared with the trial population. The PBAC considered that the improvement in overall survival was modest, that this improvement may not be realised in clinical practice, and should be considered in the context of the substantial toxicity associated with regorafenib treatment.

7.2 The PBAC considered that there is a clinical need for treatments for patients with HCC, as current outcomes are poor with a median survival of less than 8 months for the BSC arm in the RESORCE trial.

7.3 The PBAC noted that the RESORCE trial enrolled patients with an ECOG ≤1 while the current PBS listing for sorafenib is for patients with WHO PS ≤2. The PBAC considered that the listing should be for patients with WHO PS ≤1. The PBAC agreed with ESC that the most appropriate restriction is 'Patients must only be treated until disease progression' as the PBAC considered that use of regorafenib beyond progression is unlikely to be cost effective.

7.4 The PBAC agreed with ESC that the comparator of best supportive care was appropriate.

7.5 The PBAC noted that the submission was based on one head-to-head trial comparing regorafenib with BSC, RESORCE trial (n=573). The ESC noted that the PSCR also presented the updated overall survival results (cut-off date Jan 23, 2017) from the RESORCE trial, with longer follow-up. The PBAC noted that the outcomes with the updated data were consistent with those using the earlier data cut.

7.6 The PBAC noted that there were differences between the trial population and the likely eligible Australian population due to the strict inclusion criteria in the RESORCE trial. The PBAC considered that patients recruited into the RESORCE trial are likely to be younger and fitter that the Australian population for the requested listing. The PBAC considered that this is likely to impact on the applicability of the safety and efficacy outcomes from the trial to patients treated in Australia under the proposed listing.

7.7 The PBAC noted that the RESORCE trial showed a 2.8 month improvement in median survival, a 1.6 month improvement in PFS, and a 1.7 month improvement in time to progression for patients treated with regorafenib. The PBAC noted that the updated data (January 2017, 11 months after the primary analysis) indicated that the improvement in median survival was maintained. The PBAC considered that the claim of superior comparative effectiveness was reasonable and that regorafenib showed modest clinical benefit, though it was associated with substantial toxicity and no improvement in quality of life. The PBAC was concerned that the benefits observed in the RESORCE trial may be smaller in the PBS population due to their poorer prognosis and the reduced tolerability of regorafenib.

7.8 The PBAC noted that regorafenib patients are 3 times more likely to suffer any grade 3 or 4 adverse event compared to BSC. The Committee also noted a number of serious grade 5 AEs and a substantial increase in bothersome grade 1 and 2 AEs for patients treated with regorafenib. In addition, the RESORCE trial reported numerically worse average quality of life (QoL) for regorafenib compared with BSC, which may reflect the increased toxicity. The PBAC considered that the evidence presented in the submission did not support the submission's initial claim of no significant impact of regorafenib toxicity on QoL, and that the claim of inferior safety compared with BSC was appropriate. The PBAC considered that overall, regorafenib was associated with a range of substantial AEs, which may be more frequent and severe in the proposed Australian population compared with the trial population.

7.9 The PBAC noted the base case ICER presented was $15,000 - $45,000 per additional life year and $45,000 - $75,000 per QALY gained. The PBAC considered that this base case is likely to underestimate the ICER. The PBAC noted the issues identified in the commentary and raised by ESC regarding the economic analysis presented including: extrapolation of the regorafenib arm only, the arbitrary choice of inflection point for extrapolation, extrapolation from 33 months where there were very few patients at risk and use of average utility values by heath state. The PBAC also noted that the ICER was most sensitive to the time horizon, increasing the ICER by approximately 35% when reduced to 3 years in the univariate sensitivity analysis.

7.10 The Committee noted that univariate and multivariate sensitivity analyses were presented in the pre-PBAC response as requested by ESC, as well as a revised proposed price. The PBAC considered that the multivariate sensitivity analysis as specified by ESC, where OS and PFS are extrapolated from the median follow-up for both regorafenib and BSC arms, no piecewise Gompertz model for OS, and applying trial-based utilities, gave an ICER of $75,000 - $105,000 per QALY gained and $45,000 - $75,000 per QALY gained with the revised price. The PBAC considered that the ESC specifications provided the most appropriate base case for informing the ICER.

7.11 The PBAC considered that overall the financial estimates were over-estimated due to: overestimated eligible patient pool and uptake rates, inclusion of patients with ECOG PS>1, and the assumption of treatment beyond progression. The PBAC also advised that costs to the MBS should be included in the financial estimates. Overall

the PBAC considered that the financial impact of listing regorafenib is unlikely to exceed $10 million in any of the first 6 years of listing.

7.12 The PBAC acknowledged the clinical need in the proposed PBS population, and advised that a future major submission should include a lower price, giving an ICER of $15,000 - $45,000 per QALY gained to reflect the substantial toxicity, with the appropriate changes to the economic model base case as specified in paragraph 7.10. The PBAC also advised that a resubmission should be based on the latest available data from the RESORCE trial.

7.13 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

Bayer is committed to working with the PBAC to ensure the earliest possible PBS listing of Regorafenib for patients with unresectable hepatocellular carcinoma (HCC), as current outcomes are poor with liver cancer being the 6th most common cause of cancer death in males and the 9th most common cause of cancer death in females in Australia (AIHW 2017).