
Article:
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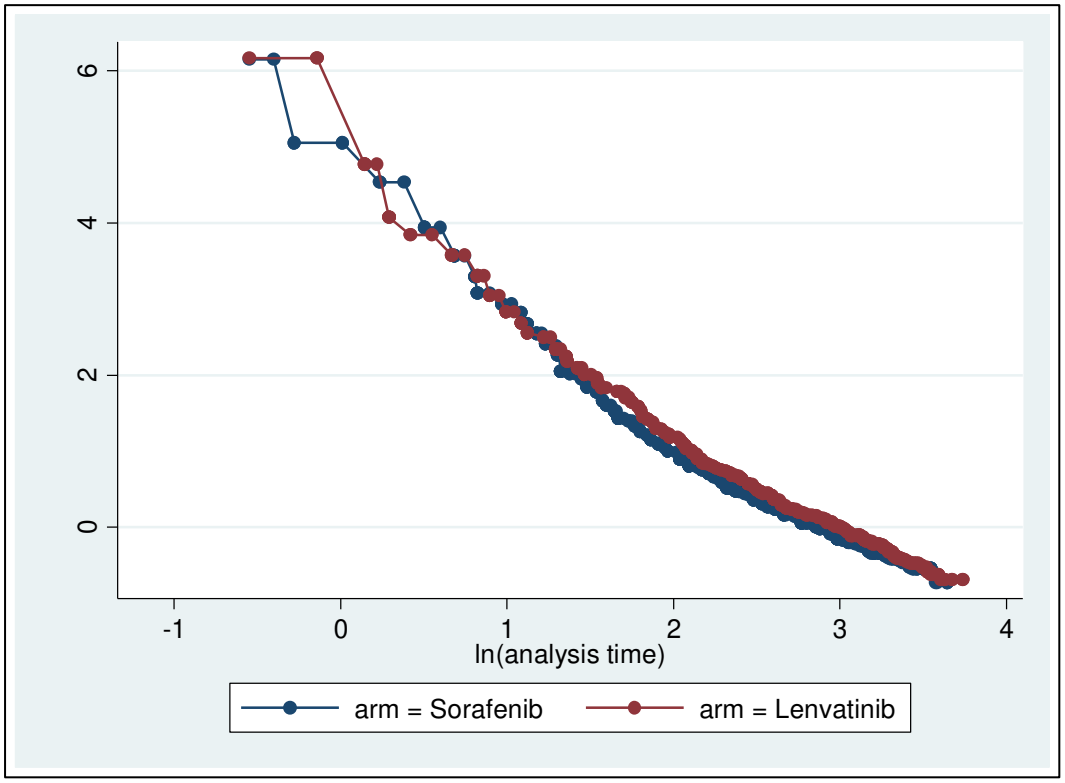
Supplementary Table 1: Comparison of original and reconstructed survival data

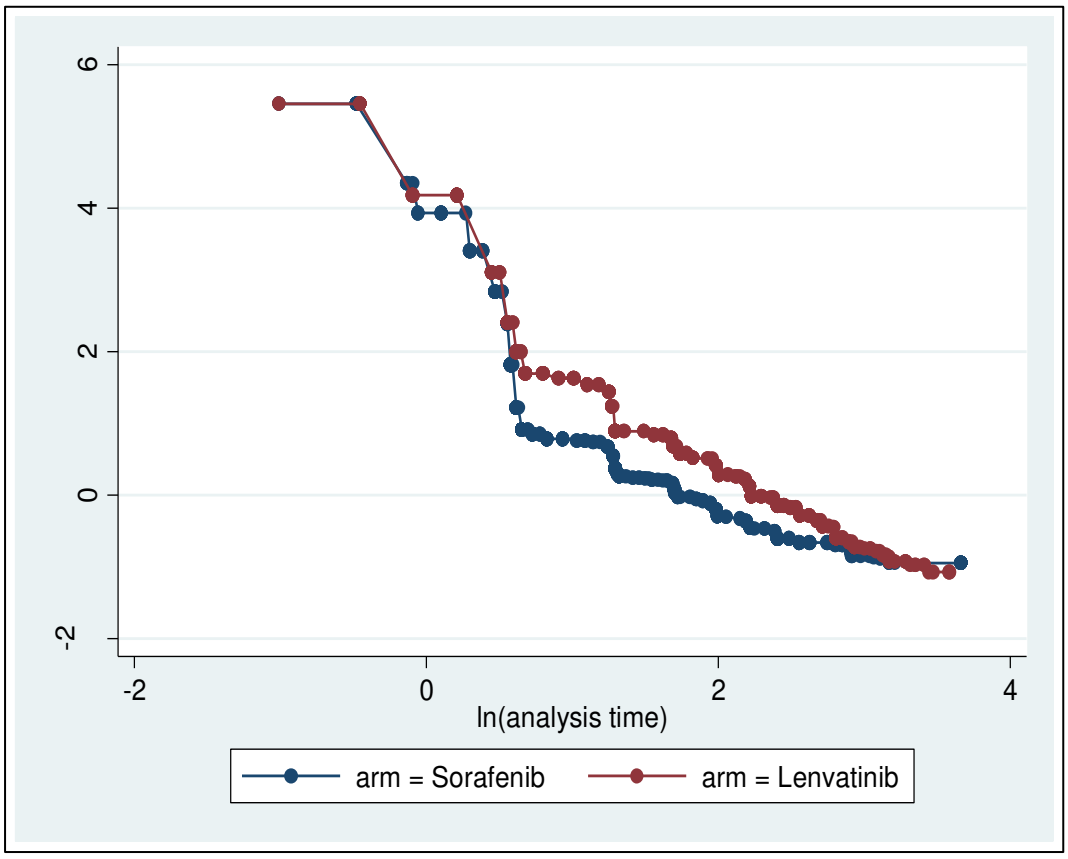
	Lenvatinib		Sorafenib	
	Original	**Reconstructed**	**Original**	**Reconstructed**
Median PFS (95% CI)	7·4 (6·9 - 8·8)	7.42 (6.9 - 8.8)	3·7 (3·6 - 4·6)	3.71 (3.6 - 4.5)
HR (95% CI)	0·66 (0·57- 0·77)	0.67 (0.58 - 0.78)	Reference	Reference
Median OS (95% CI)	13.6 (12.1 - 14.9)	13.9 (12.2 - 14.2)	12.3 (10.4 - 13.9)	12.0 (10.7 -15.4)
HR (95% CI)	0·92 (0·79 - 1.06)	0.903 (0.78 - 1.05)	Reference	Reference

CI confidence interval, *HR* hazard ratio, *PFS* progress-free survival, OS overall survival.

Supplementary Figure 1: Log-cumulative hazard plot for OS



Supplementary Figure 2: Log-cumulative hazard plot for PFS



Supplementary Table 2: Parameters of distributions to extrapolate the long-term OS and PFS

Drug	Distribution	Parameter	Mean	95% CI	SE
PFS					
Lenvatinib	Lognormal	_cons	1.957	(1.86 to 2.05)	0.047
		sigma (ancillary parameter)	0.964	(0.89 to 1.03)	0.037
Sorafenib	Loglogistic	_cons	1.454	(1.44 to 1.63)	0.048
		gamma (scale parameter)	0.569	(0.52 to 0.61)	0.024
OS					
Lenvatinib	Lognormal	_cons	2.636	(2.54 to 2.74)	0.049
		sigma (ancillary parameter)	0.995	(0.92 to 1.07)	0.039
Sorafenib	Loglogistic	_cons	2.528	(2.41 to 2.62)	0.048
		gamma (scale parameter)	0.581	(0.53 to 0.63)	0.024

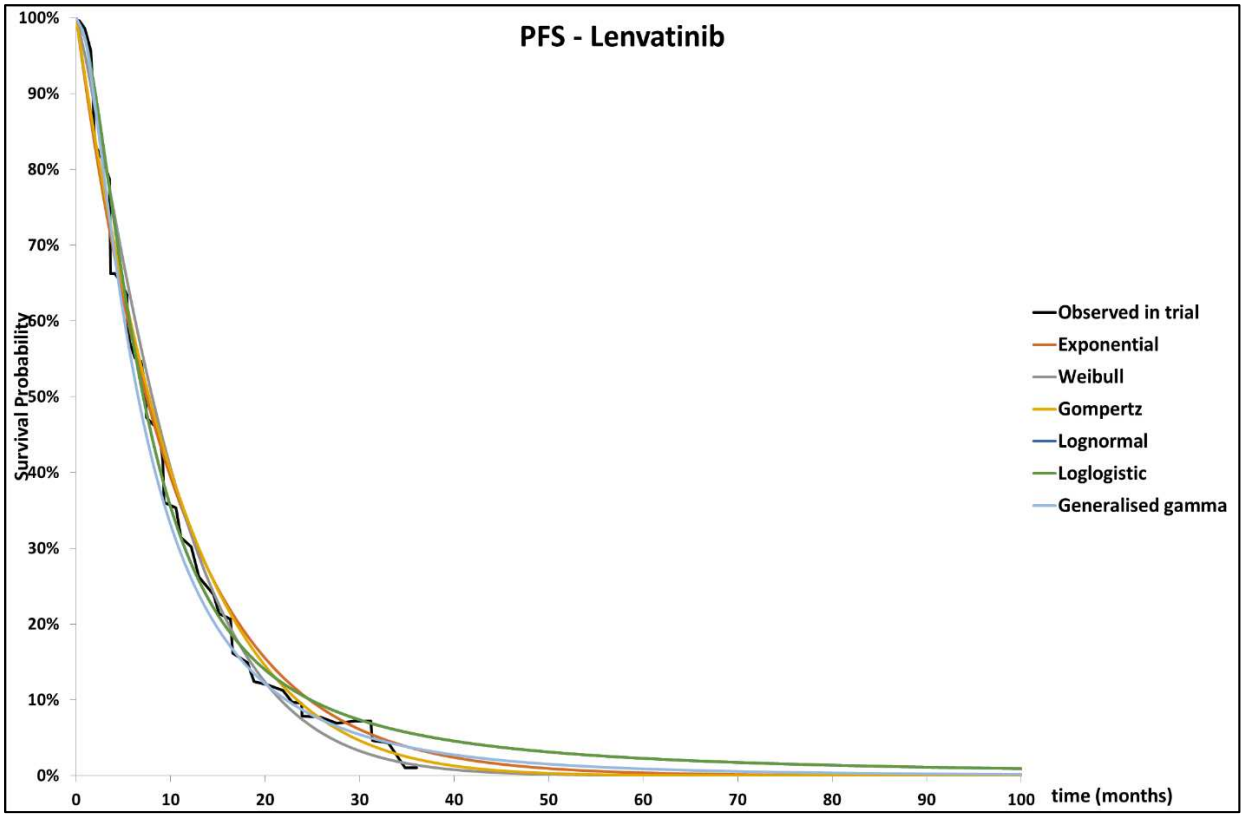
OS overall survival, *PFS* progression-free survival, *std* standard, *_cons* regression coefficient for hazard rate, *CI* confidence interval; *SE* standard error

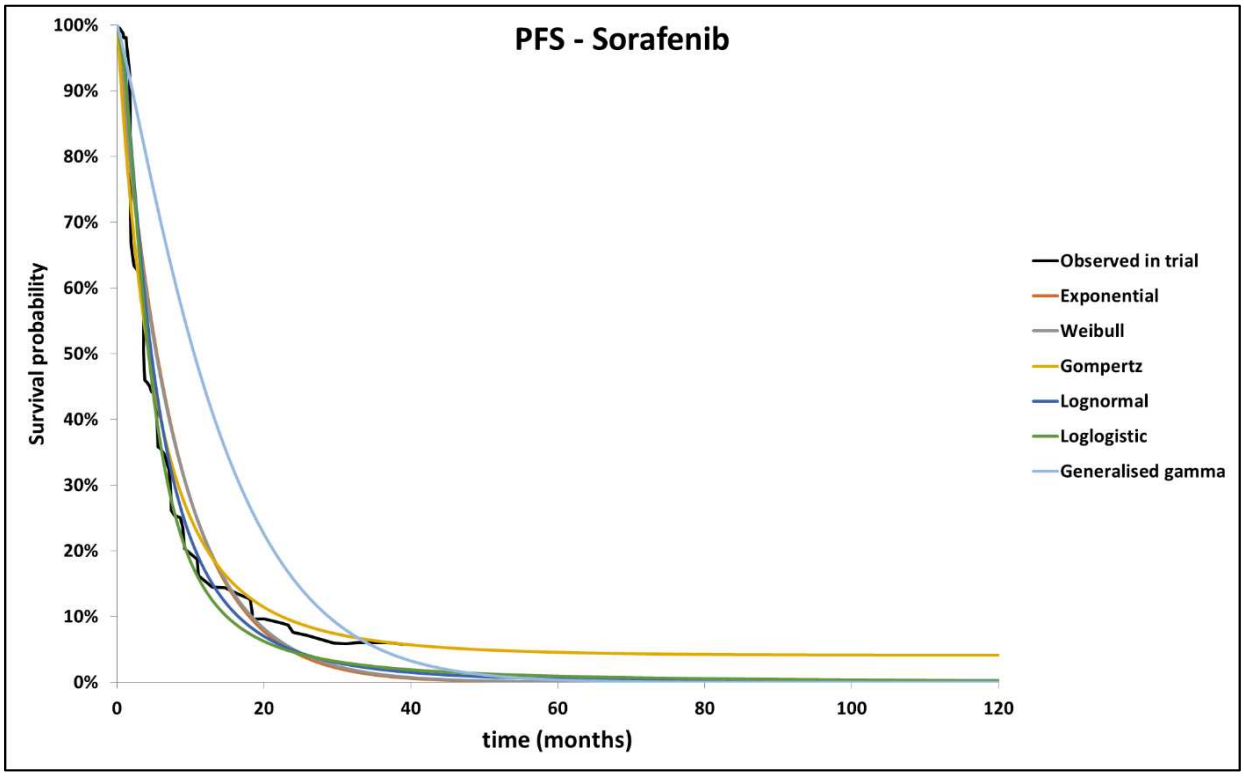
Supplementary Table 3: Parameters of distributions to extrapolate OS and PFS

Drug	Survival Distribution	PFS		OS	
		AIC	BIC	AIC	BIC
Lenvatinib	Exponential	1176	1181	1246	1250
	Weibull	1158	1166	1222	1230
	Gompertz	1176	1184	1242	1250
	Lognormal	1118	1127	1197	1205
	Loglogistic	1131	1140	1202	1211
	Generalised gamma	1120	1133	1199	1211
Sorafenib	Exponential	1349	1353	1242	1246
	Weibull	1350	1358	1223	1231
	Gompertz	1294	1302	1242	1250
	Lognormal	1207	1215	1191	1199
	Loglogistic	1206	1214	1184	1192
	Generalised gamma	1141	1153	1185	1197

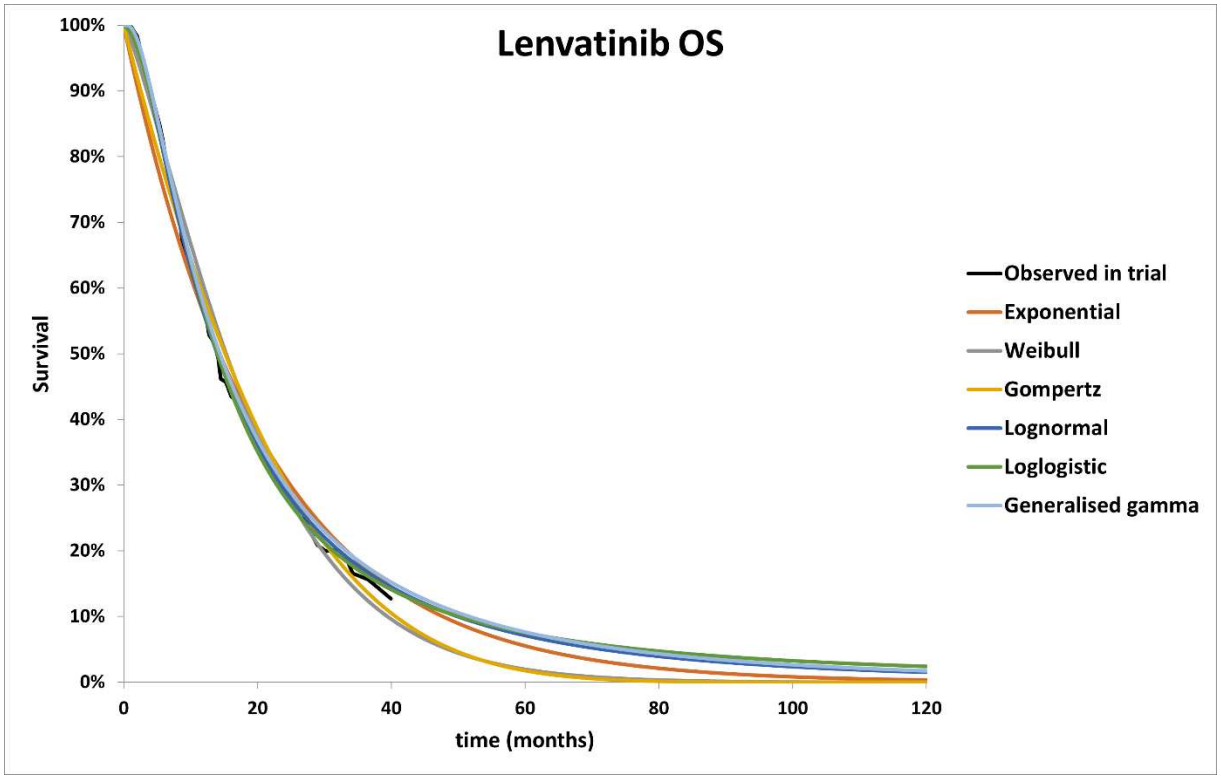
AIC Akaike information criteria*, BIC* Bayesian information criteria*, OS* overall survival, *PFS* progression-free survival

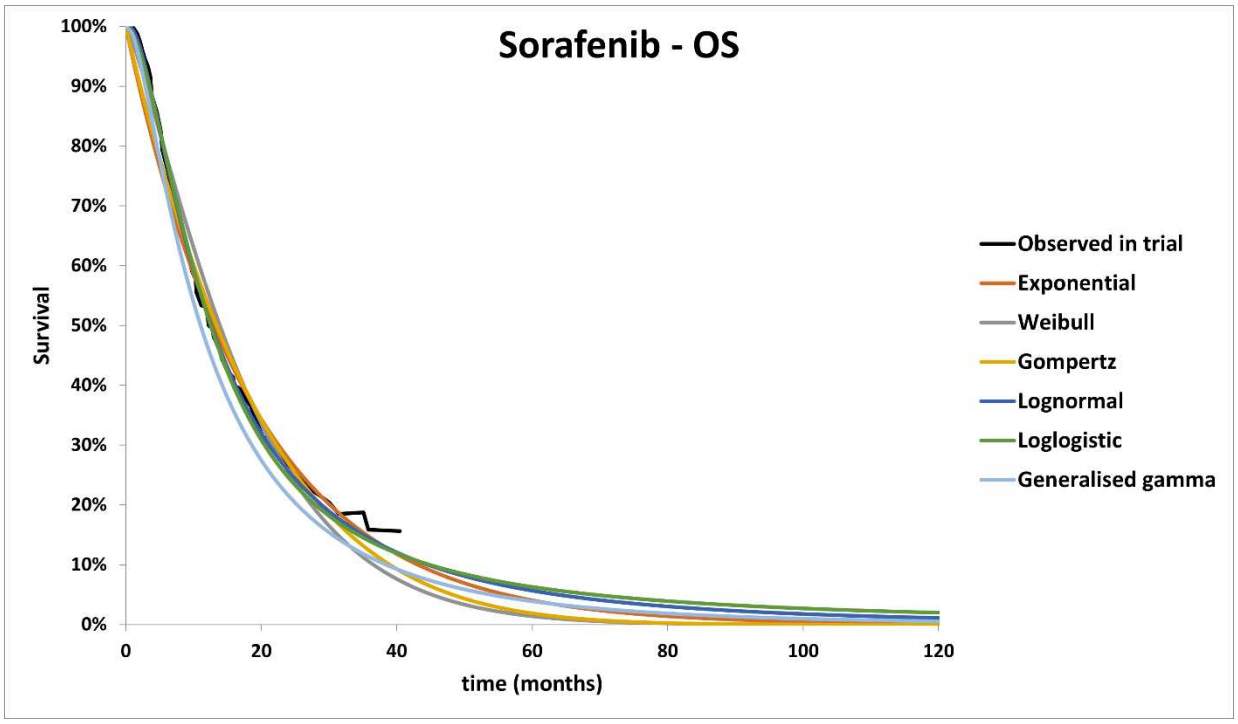
Supplementary Figure 3: Fitted parametric PFS survival function to trial data



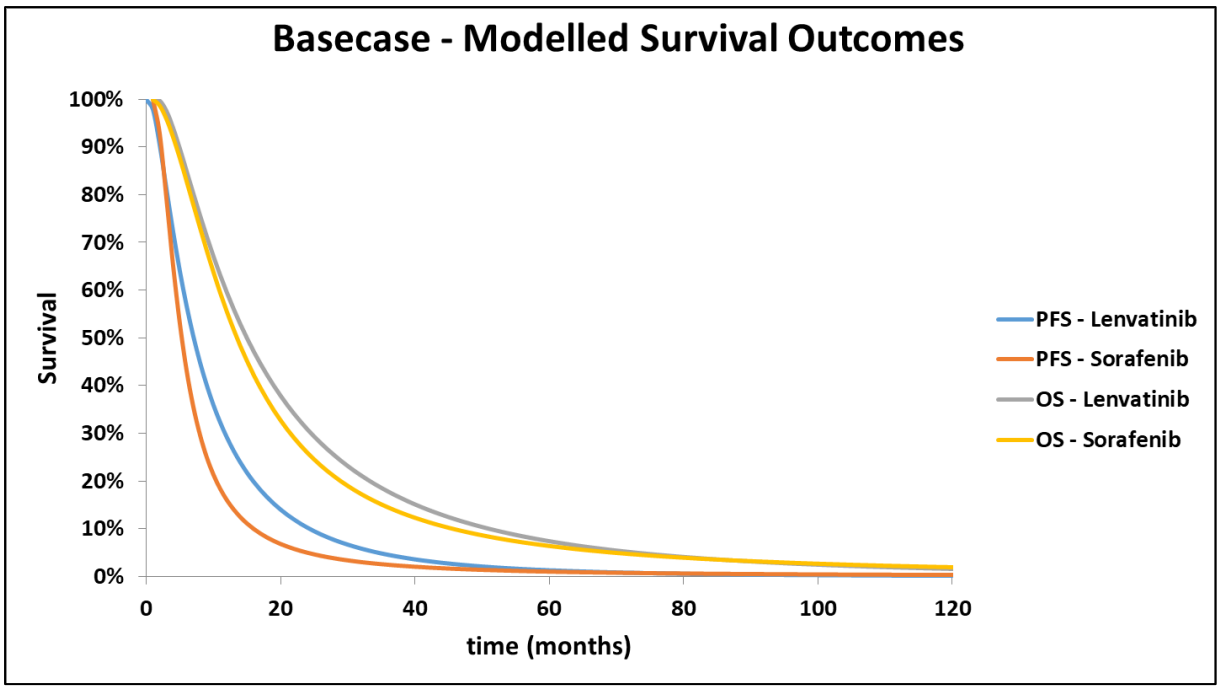


Supplementary Figure 4: Fitted parametric OS survival function to trial data





Supplementary Figure 5: Modelled survival outcomes in base case



Supplementary Table 4: Unit cost of adverse events

Grade ≥ 3 Adverse events	**Unit**	**Source***	**Unit cost**
Elevated Aspartate amino transferase	Per hospitalization	AR-DRG H63-A, B, C	$6677
Appetite decreased	Per hospitalization + Dietician visit	AR-DRG K62-C	$884
Elevated Blood bilirubin	Per hospitalization	AR-DRG H63-A, B, C	$6677
Diarrhoea	Per hospitalization	AR-DRG G70-A, B	$3569
Fatigue	Per hospitalization	AR-DRG Q61B	$1679
Nausea/vomiting	Per hospitalization	AR-DRG K62-C	$884
Hypertension	Per hospitalization	AR-DRG H63-A, B, C	$6677
Palmar-plantar erthrodysaesthesia syndrome	Per hospitalization	AR-DRG J68-A, B	$4215
Platelet count decreased	Per hospitalization	AR-DRG Q60-B	$1741
Proteinuria	Per hospitalization	AR-DRG L65-B	$2371
Weight decreased	Per hospitalization + Dietician visit	AR-DRG K62-C	$884

ARGDRG Australian Refined Diagnosis Related Groups,
* Hospital Cost Data Collection, Public Hospitals Cost Report, available at https://www.ihpa.gov.au/what-we-do/nhcdc.

Supplementary Table 5: Disutility with adverse events

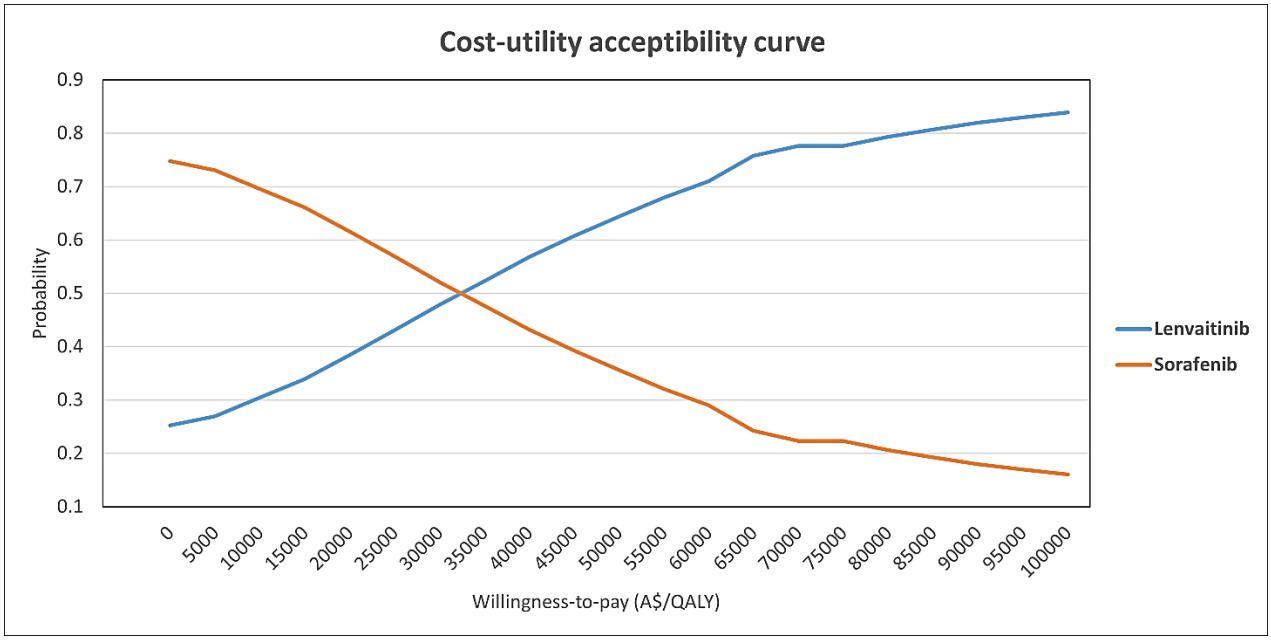
Adverse event	Disutility	QALY decrement - Lenvatinib	QALY decrement - Sorafenib	Source
Diarrhoea	-0.05	-0.002	-0.002	[19]
Fatigue	-0.07	-0.0028	-0.0028	[19]
Nausea/vomiting	-0.05	-0.001	-0.001	[19]
Hypertension	-0.012	-0.00276	-0.00168	[19]
PPE syndrome	-0.116	-0.00348	-0.01276	[18]

PPE Palmar-plantar erthrodysaesthesia, *QALY* quality-adjusted life years

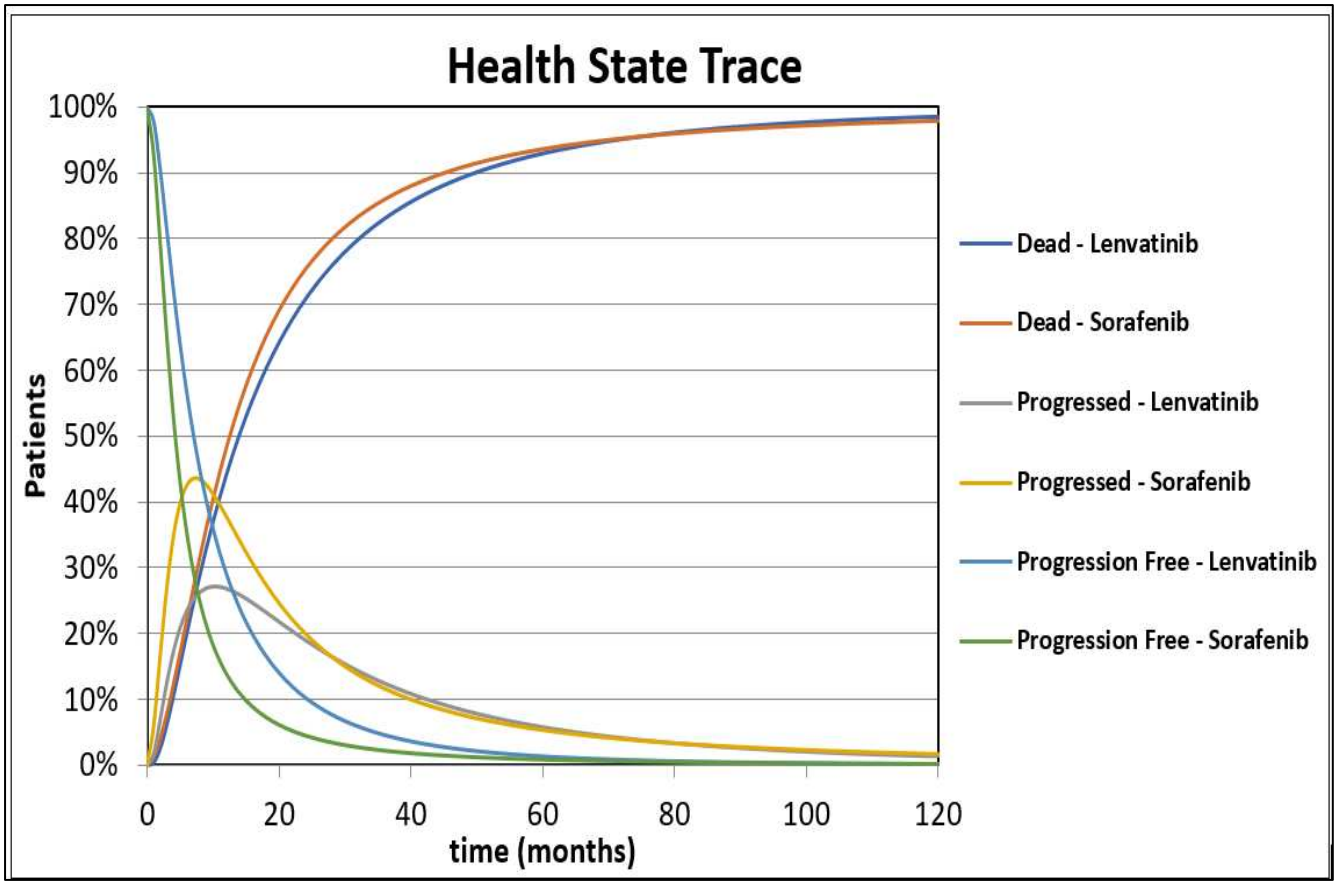
Supplementary Table 6: Distribution for the parameters in the probabilistic sensitivity analyses

Variable	Distribution	Alpha	Beta
Cost of management for the PF state	Gamma	4445	0.2
Cost of management for the PD state	Gamma	10000	0.21
Cost of End-of-life	Gamma	3460	79
Utility of PF	Beta	2416	827
Utility of PD	Beta	1074	510
Dose intensity - lenvatinib	Beta	12	1.6
Dose intensity - sorafenib	Beta	17	3.4
PFS parametric function (scale & shape parameter)	Multivariate-normal distribution	-	-
OS parametric function (scale & shape parameter)	Multivariate-normal distribution	-	-

PF: progression free; PD: progressed disease



Supplementary Figure 6: Cost-utility acceptability curve



Supplementary Figure 7: Health state traces of the partitioned survival model.

Supplementary Table 7: Comparison of Partitioned Survival model and REFLECT trial

Outcome	Model		REFLECT trial	
	Lenvatinib	Sorafenib	Lenvatinib	Sorafenib
Median PFS (months)	7.5	4.0	7.4	3.7
Median OS (months)	14.0	12.5	13.6	12.3

PFS progression-free survival, *OS* overall survival

Supplementary Table 8: Calculation of unit cost of treatment cycles

Component	Calculation	Lenvatinib	Sorafenib
Max quantitity pack (A)	-	3	2
units per pack (B)	-	30	60
dose per unit (C)	-	4 mg	200 mg
total dose per pack (D)	D = B x C	120 mg	12000 mg
AEMP($) per pack (E)[a]	-	$1,840	$2,997
Cost per mg (F)	F = E/D	$15.3	$0.2
Recommended dose (G)	-	10.72 mg[b]	800 mg
Dose intensity (H)	-	88%	83%
mean dose per day (I)	I = G x H	9.4336 mg	664 mg
cost per day (J)	J = F x I	$145	$166
cost per 28-day cycle (K)	K = J x 28	$4,050	$4,643

[a] The AEMP prices per pack for both drugs are available footnote and within the Table 1 at https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-11/files/lenvatinib-psd-november-2018.pdf.

[b]Based on the REFLECT trial, 32% patients (<60 kg body weight) get 8mg and 68% (>60 kg body weight get 12 mg, therefore, recommended dose for Lenvatinib is 10.72 mg [(0.32x8mg) + (0.68x12mg)].

AEMP approved ex-manufacturer price*; mg* miligrams

Supplementary Table 9: Comparison of present study with previous studies.

Key feature(s)	Current study	NICE submission [7]	Kim et al [21]	Kobayashi et al [22]
County focus	Australia	United Kingdom	Canada	Japan
Survival estimates used in the model from REFLECT	ITT	Post hoc: analysis: Covariates adjusted using the corrected group prognosis method	ITT	AFP-adjusted population
Modelling approach	PSM	PSM	Markov	PSM
Time horizon	10 years	20 years	5 years	65 years
PFS distribution	Log-normal	Log-normal	S: Log-normal; L: Log-logistic	Log-normal
OS distribution	Log-logistic	Log-logistic	S: Log-normal; L: Log-logistic	Log-logistic
Cycle length	1 month	1 month	1 month	1 month
Discount rate	5%	3.5%	1.5%	2%
Drug cost (per cycle)	L: AU$4050 S: AU$4643	L: NA S: £2,968.	L: CA$2,735 S: CA$5,476	L: JPY 263,861 S: JPY 436,180
Health Utility - PF	0.745	0.745	0.760	on-trt.: 0.845; off-trt.: 0.832 (L) & 0.837 (S)
Health Utility - PD	0.678	0.678	0.680	0.714

AFP alpha-fetoprotein; *AU* Australian *CA* Canadian*; ITT* intention-to-treat*; L* Lenvatinib*; NICE* National Institute for Health and Care Excellence; *PSM* partitioned survival model; *PFS* progression-free survival; *PF* progression- free; *PD* progressed disease; *S* sorafenib; *trt* treatment; *OS* overall survival; *NA* not available; *JPY* Japanese yen

Supplementary Table 10: Reconstructed Kaplan-Meier survival probabilities

Progression-free survival				Overall survival			
Lenvatinib		Sorafenib		Lenvatinib		Sorafenib	
Time (months)	Cumulative Survival Probability	Time (months)	Cumulative Survival Probability	Time (months)	Cumulative Survival Probability	Time (months)	Cumulative Survival Probability
0.0	100%	0.0	100%	0.0	100%	0.0	100%
0.4	100%	0.4	100%	1.1	100%	1.1	100%
0.9	99%	0.9	99%	2.0	98%	1.7	99%
1.6	96%	0.9	98%	2.7	96%	2.1	97%
1.7	91%	1.3	98%	3.5	93%	2.4	96%
1.9	87%	1.3	97%	4.3	89%	2.8	95%
2.0	83%	1.6	94%	4.9	87%	3.3	93%
2.5	82%	1.7	92%	5.3	85%	3.6	92%
3.0	81%	1.7	90%	5.8	83%	3.8	88%
3.5	79%	1.8	87%	6.5	79%	4.5	86%
3.6	75%	1.8	83%	7.1	76%	5.1	82%
3.6	66%	1.9	77%	7.8	73%	5.4	79%
4.1	66%	1.9	71%	8.4	69%	5.8	78%
4.8	65%	1.9	67%	8.9	66%	6.2	76%
5.4	63%	2.1	65%	9.4	64%	6.7	73%
5.4	60%	2.3	63%	10.2	62%	7.2	71%
5.7	57%	2.8	63%	10.7	61%	7.5	68%
6.2	55%	3.1	62%	11.6	59%	7.9	67%
6.9	55%	3.5	60%	12.3	56%	8.2	64%
7.3	52%	3.6	57%	12.7	53%	8.7	63%
7.4	47%	3.6	54%	13.5	52%	9.3	61%
8.3	46%	3.6	50%	14.1	49%	9.7	59%
8.8	45%	3.7	48%	14.5	46%	10.3	58%
9.2	42%	3.8	46%	15.3	46%	10.4	56%
9.3	36%	4.1	46%	16.1	44%	10.7	55%
10.6	35%	4.5	45%	16.9	43%	11.2	53%
11.1	31%	4.7	44%	17.7	42%	11.8	53%
12.2	30%	5.1	44%	18.6	40%	12.0	52%
13.0	26%	5.4	43%	19.3	38%	12.2	50%
14.6	24%	5.4	42%	20.3	37%	12.7	50%
15.1	21%	5.5	40%	21.0	34%	13.0	48%
16.3	21%	5.5	38%	22.0	33%	13.2	48%
16.6	16%	5.6	36%	22.9	32%	13.8	46%
18.1	15%	5.8	36%	23.8	30%	14.2	44%
18.8	12%	6.4	35%	24.7	29%	14.9	43%
20.2	12%	6.7	34%	25.4	28%	15.8	41%
21.8	11%	7.0	32%	26.3	27%	16.1	40%
22.9	10%	7.3	29%	27.0	25%	16.6	40%
23.8	10%	7.4	26%	27.8	24%	17.1	39%
23.9	8%	7.8	25%	28.3	22%	17.6	38%
25.9	8%	8.6	25%	28.9	21%	18.4	37%
27.6	7%	9.0	24%	30.2	20%	19.0	35%
29.4	7%	9.2	20%	32.0	20%	19.7	33%
31.2	7%	9.5	20%	33.1	19%	20.2	32%
31.4	5%	10.9	19%	34.2	17%	20.9	31%
33.0	4%	11.1	16%	36.5	16%	21.7	30%
34.8	1%	12.9	14%	40.0	13%	22.7	28%
36.0	1%	14.7	14%	-	-	24.0	27%
-	-	16.5	13%	-	-	25.3	25%
-	-	18.1	13%	-	-	26.0	24%
-	-	18.4	11%	-	-	27.3	23%
-	-	18.4	10%	-	-	28.6	22%
-	-	19.2	10%	-	-	30.0	20%
-	-	20.1	10%	-	-	31.4	19%
-	-	21.5	9%	-	-	35.1	19%
-	-	22.5	9%	-	-	35.8	16%

-	-	23.3	9%	-	-	40.5	16%
-	-	23.9	8%	-	-	-	-
-	-	25.8	7%	-	-	-	-
-	-	29.5	6%	-	-	-	-
-	-	31.2	6%	-	-	-	-
-	-	32.8	6%	-	-	-	-
-	-	36.9	6%	-	-	-	-
-	-	39.0	6%	-	-	-	-