ERRATA

1. Nature of the error and how it was resolved

The Assessment Group (AG) report included results from random effects network meta-analysis (NMA) models for time to first on-study SRE and risk of first-and-subsequent SRE that were misspecified, resulting in credible intervals that were overly narrow. Diagnostics of the correctly specified random effects models showed that random effects models were suboptimal for the data on these outcomes. We have rerun the models for time to first on-study SRE and risk of first-and-subsequent SREs as fixed effects models. The effect sizes have changed little but the credible intervals are wider and more consistent with those quoted by the manufacturer. Diagnostics show these models are now more stable, but the previously quoted cautious interpretation still stands. Tables that required updating are listed below along with page numbers from the Assessment Group report.

2. Clinical effectiveness

2.1 AG NMA numbers that have changed

- **Breast cancer**

Table 17 Time to first on-study SRE (p62)

Comparison	**AG NMA HR (95% CI)**	**MS NMA HR (95% CI)**
Denosumab versus zoledronic acid	0.82 (0.71 to 0.95)	[redacted]
Denosumab versus pamidronate	0.79 (0.61 to 1.03)	[redacted]
Denosumab versus placebo	0.46 (0.29 to 0.72)	[redacted]
Zoledronic acid versus placebo	0.56 (0.36 to 0.86)	[redacted]
Denosumab versus ibandronic acid	Not performed	[redacted]

Table 18 Risk of first-and-subsequent on-study SRE (p63)

Comparison	**AG NMA RR (95% CI)**	**MS NMA RR (95% CI)**
Denosumab versus zoledronic acid	0.77 (0.66 to 0.89)	[redacted]
Denosumab versus pamidronate	0.62 (0.48 to 0.80)	[redacted]
Denosumab versus placebo	0.45 (0.28 to 0.72)	[redacted]
Zoledronic acid versus placebo	0.59 (0.37 to 0.91)	[redacted]
Denosumab versus ibandronic acid	Not performed	[redacted]

- **Prostate cancer**

Table 33 Time to first on-study SRE (pp 84)

	AG NMA **HR (95%CI)**	**MS NMA** **HR (95%CI)**
Denosumab versus zoledronic acid	0.82 (0.71 to 0.95)	[redacted]
Denosumab versus placebo	0.56 (0.40 to 0.77)	[redacted]
Zoledronic acid versus placebo	0.68 (0.50 to 0.91)	[redacted]

Table 34 Risk of first-and-subsequent on-study SREs (p85)

	AG NMA **RR (95%CI)**	**MS NMA** **RR (95%CI)**
Denosumab versus zoledronic acid	0.82 (0.71 to 0.94)	[redacted]
Denosumab versus placebo	0.53 (0.39 to 0.72)	[redacted]
Zoledronic acid versus placebo	0.64 (0.48 to 0.85)	[redacted]

- **Non-small cell lung cancer (NSCLC)**

Table 40 Time to first on-study SRE (p96)

	AG NMA **HR (95%CI)**
Denosumab versus zoledronic acid	0.84 (0.64 to 1.10)
Denosumab versus placebo	0.68 (0.45 to 1.03)
Zoledronic acid versus placebo	0.81 (0.59 to 1.11)

Table 41 Risk of first-and-subsequent SREs (p96)

	AG NMA **RR (95%CI)**
Denosumab versus zoledronic acid	0.87 (0.68 to 1.12)
Denosumab versus placebo	0.63 (0.42 to 0.97)
Zoledronic acid versus placebo	0.73 (0.52 to 1.02)

- **Other solid tumours (excluding NSCLC)**

Table 43 Time to first on-study SRE (p102)

	AG NMA **HR (95%CI)**
Denosumab versus zoledronic acid	0.79 (0.62 to 0.99)
Denosumab versus placebo	0.30 (0.11 to 0.82)
Zoledronic acid versus placebo	0.37 (0.14 to 1.01)

Table 44 Risk of first-and-subsequent SREs (p102)

	AG NMA **RR (95%CI)**
Denosumab versus zoledronic acid	0.83 (0.67 to 1.03)
Denosumab versus placebo	0.61 (0.39 to 0.97)
Zoledronic acid versus placebo	0.74 (0.49 to 1.10)

- **Other solid tumours (including NSCLC)**

Table 55 Time to first on-study SRE (p118)

	AG NMA **HR (95%CI)**	**MS NMA** **HR (95%CI)**
Denosumab versus zoledronic acid	0.81 (0.68 to 0.96)	[redacted]
Denosumab versus placebo	0.49 (0.30 to 0.78)	[redacted]
Zoledronic acid versus placebo	0.60 (0.38 to 0.93)	[redacted]

Table 56 Risk of first-and-subsequent on-study SREs (p119)

	AG NMA **RR (95%CI)**	**MS NMA** **HR (95%CI)**
Denosumab versus zoledronic acid	0.85 (0.72 to 1.00)	[redacted]
Denosumab versus placebo	0.62 (0.46 to 0.85)	[redacted]
Zoledronic acid versus placebo	0.73 (0.56 to 0.95)	[redacted]

2.2 Implications of the error for the results and conclusions in the assessment report

(a) Implications for the results

- **Breast cancer**

Time to first on-study SRE

For the comparison of denosumab with pamidronate, the result has changed from being statistically significant to no longer being statistically significant although the direction of effect still favours denosumab.

- **NSCLC**

Time to first-on-study SRE

For the comparisons of denosumab versus zoledronic acid, and denosumab versus placebo, the results have changed from being statistically significant to no longer being statistically significant, although the direction of effect still favours denosumab. For the comparison of zoledronic acid versus placebo, the result has changed from being statistically significant to no longer being statistically significant, although the direction of effect still favours zoledronic acid.

Risk of first-and-subsequent SREs

For the comparison of zoledronic acid versus placebo, the result has changed from being statistically significant to no longer being statistically significant, although the direction of effect still favours zoledronic acid.

- **Other solid tumours (excluding NSCLC)**

Time to first on-study SRE

For the comparison of zoledronic acid versus placebo, the result has changed from being statistically significant to no longer being statistically significant, although the direction of effect still favours zoledronic acid.

Risk of first-and subsequent SREs

For the comparison of denosumab versus zoledronic acid, the result has changed from being statistically significant to no longer being statistically significant, although the direction of effect still favours denosumab. For the comparison of zoledronic acid versus placebo, the result has changed from being statistically significant to no longer being statistically significant, although the direction of effect still favours zoledronic acid.

- **Other solid tumours (including NSCLC)**

Risk of first-and-subsequent SREs

For the comparison of denosumab versus zoledronic acid, the result has changed from being statistically significant to no longer being statistically significant (upper CI now 1.00), although the direction of effect still favours denosumab.

(b) Implications for the conclusions

All comparisons involving denosumab for time to first on-study SRE and risk of first-and-subsequent SREs still favour denosumab, but whereas previously one did not reach statistical significance (NSCLC, risk of first-and-subsequent SREs, denosumab versus zoledronic acid), now six no longer reach statistical significance:

- Breast cancer

Time to first on-study SRE - denosumab versus pamidronate

- NSCLC

Time to first on-study SRE – denosumab versus zoledronic acid; denosumab versus placebo
Risk of first-and-subsequent SREs – denosumab versus zoledronic acid

- OST (excluding NSCLC)

Risk of first-and-subsequent SREs – denosumab versus zoledronic acid

- OST (including NSCLC)

Risk of first-and-subsequent SREs – denosumab versus zoledronic acid

These changes do not affect our conclusions in relation to the NMA in that the results of the NMA are subject to considerable uncertainty and should be interpreted with caution.

3. Cost-effectiveness

3.1 Numbers that have changed

The principal erratum relates to the AG NMA moving from a random effects model to a fixed effects model. This has the benefit of the base case modelling that applies the AG fixed effects NMA being consistent with the head to head results of the trials for the effectiveness of denosumab versus zoledronic acid.

There was also an erratum relating to not applying the RCT data on the durations of ONJ SAEs and renal SAEs in the base case. This has been addressed in what follows.

The simplistic trial based analyses of tables 102 on p194, 103 on p195, 104 and 105 on p196 are not affected by the revised AG NMA.

All the remaining health economic results are affected, including all of Appendix 15. Given the extent of this the table of economics errata identifies the text that has to be changed and presents a revised version but it only identifies the tables and figures that require revision. The revised tables and figures are presented at the foot of this document.

Appendix 15 has been revised in its entirety and is presented at the foot of this document.

3.2 Implications of the error for the results and conclusions in the assessment report

(a) Implications for the results

- **Breast cancer**

Across all patients the modelled reduction in SREs from denosumab over BSC and over zoledronic acid falls slightly. The anticipated patient benefits over zoledronic acid are reduced by around one third, with a proportion of this reduction being due to the revised SAE data. The cost effectiveness of denosumab relative to BSC is only marginally affected, but the ICER for denosumab ex PAS relative to zoledronic acid worsens to £245k. With the PAS denosumab is still estimated to be cost saving relative to zoledronic acid, though this saving falls from £270 to £243, and so to dominate zoledronic acid.

- **Prostate cancer**

Across all patients the modelled reductions in SREs from denosumab over BSC and over zoledronic acid fall. This is most notable relative to zoledronic acid where the net gain falls from 0.228 SREs to 0.130 SREs. The patient benefits for denosumab relative to BSC are reasonably stable, but for denosumab relative to zoledronic acid are approximately halved which roughly doubles the ICER to £111,603 per QALY. With the PAS denosumab is still estimated to be cost saving relative to zoledronic acid, though this falls from £243 to £125, and so to dominate zoledronic acid.

- **Other solid tumours (including NSCLC)**

Across all patients the modelled reductions in SREs from denosumab over BSC and over zoledronic acid increase slightly. The patient benefits for denosumab relative to BSC increase slightly from 0.013 QALYs to 0.017 QALYs, but while they are reasonably stable relative to zoledronic acid they are estimated to fall slightly from 0.008 QALYs to 0.006 QALYs due to the revised SAE data. The ex PAS ICER for denosumab relative to BSC improves from £198k per QALY to £147k per QALY, but relative to zoledronic acid worsens from £116k per QALY to £140k per QALY. With the PAS the cost effectiveness of denosumab relative to BSC improves from £137k per QALY to £102k per QALY, and relative to zoledronic acid improves from £12,969 per QALY to £9,004 per QALY.

- **NSCLC**

The NSCLC modelling broadly mirrors the OST+NSCLC modelling. Across all patients the modelled reductions in SREs from denosumab over BSC and over zoledronic acid increase slightly. The patient benefits for denosumab relative to BSC increase slightly from 0.009 QALYs to 0.012 QALYs, but while they are reasonably stable relative to zoledronic acid they are estimated to fall slightly from 0.006 QALYs to 0.005 QALYs due to the revised SAE data. The ex PAS ICER for denosumab relative to BSC improves from £263k per QALY to £191k per QALY, but relative to zoledronic acid worsens from £128k per QALY to £150k per QALY. With the PAS the cost effectiveness of denosumab relative to BSC improves from £186k per QALY to £134k per QALY, and relative to zoledronic acid improves from £10,099 per QALY to £5,972 per QALY.

The main impact in terms of cost effectiveness is within the SRE experienced sub-group modelling for whom the cost effectiveness of denosumab relative to zoledronic acid improves from £42,698 per QALY to £12,743 per QALY.

(b) Implications for the conclusions

Within the conclusions while the formal cost effectiveness estimates have changed, with the exception of the NSCLC SRE experienced subgroup analysis the qualitative conclusions are broadly unaffected.

Appendix Changes that need to be made to the assessment report

Clinical effectiveness errata

Page number	Section/ Table	Text in AR	Correction
xxi	2	…the Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.48, 95% CI 0.46 to 0.51; HR 0.45, 95% CI 0.43 to 0.48; and HR 0.44, 95% CI 0.42 to 0.46 respectively) and risk of first-and subsequent SREs (RR 0.42, 95% CI 0.41 to 0.43; RR 0.56, 95% CI 0.54 to 0.58; RR 0.63, 95% CI 0.61 to 0.66 respectively), … For NSCLC, and other solid tumours excluding NSCLC, the Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.66, 95% CI 0.63 to 0.68 and HR 0.37, 95% CI 0.35 to 0.39 respectively) and risk of first-and-subsequent SREs (RR 0.69, 95% CI 0.66 to 0.73 and RR 0.67, 95% CI 0.64 to 0.70 respectively).	…the Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.46, 95% CI 0.29 to 0.72; HR 0.56, 95% CI 0.40 to 0.77; and HR 0.49, 95% CI 0.30 to 0.78 respectively) and risk of first-and subsequent SREs (RR 0.45, 95% CI 0.28 to 0.72; RR 0.53, 95% CI 0.39 to 0.72; RR 0.62, 95% CI 0.46 to 0.85 respectively),… For NSCLC, ~~and other solid tumours excluding NSCLC, the Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.66, 95% CI 0.63 to 0.68 and HR 0.37, 95% CI 0.35 to 0.39 respectively) and risk of first-and-subsequent SREs (RR 0.69, 95% CI 0.66 to 0.73 and RR 0.67, 95% CI 0.64 to 0.70 respectively).~~ the Assessment Group's NMA comparison of denosumab with placebo favoured denosumab without being statistically significant for time to first on-study SRE (HR 0.68, 95% CI 0.45 to 1.03) while there was a statistically significant difference in favour of denosumab for risk of first-and-subsequent SREs (RR 0.63, 95% CI 0.42 to 0.97). For other solid tumours excluding NSCLC, the Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE (HR 0.30, 95% CI 0.11 to 0.82) and risk of first-and-subsequent SREs (RR 0.61, 95% CI 0.39 to 0.97).
28-29	5.5	For time to first SRE, the random effects NMA method proposed by Woods[69] of modelling hazard ratios on the log hazard scale was adopted. One hundred thousand Markov chain Monte simulations were used in the analysis with a thinning parameter of 10 and a burn-in of 100,000. The trial data included in the model comprised log hazard ratios and its standard error. Pairwise hazard ratios were estimated from the median of the posterior distribution. The analyses included very few trials, so confidence intervals were bootstrapped to address the small amount of data. The same approach was taken for modelling rate ratios in the analysis of time to first and subsequent SREs. For SMR and proportions of patients with an SRE,	~~For time to first SRE, the random effects NMA method proposed by Woods[69] of modelling hazard ratios on the log hazard scale was adopted. One hundred thousand Markov chain Monte simulations were used in the analysis with a thinning parameter of 10 and a burn-in of 100,000.~~ Fixed effects models were used for time to first SRE, adopting an approach recommended by the NICE Decision Support Unit[69] for modelling trial-based summary measures, which can be applied to modelling hazard ratios on the log hazard scale. The trial-level data included in the models comprised log hazard ratios and its standard error. Where hazard ratios were not reported or derivable in the primary study, Kaplan-Meier estimates and numbers at risk (if available) were used, applying the methods of

		random effects models were also used. The data included in the SMR models were mean SMR and standard deviation along with the number of patients. For the proportions with an SRE, the numbers of patients and the numbers with an SRE were used. In the SMR and proportion models, median estimates were taken from 10,000 MCMC simulations after a burn-in of 10,000, with lower and upper 95% confidence limits taken from 2.5% and 97.5% percentiles respectively. Zoledronic acid was treated as the baseline comparator in each analysis as it is the treatment common to the largest number of trials and is present in multiple included studies for each NMA. Vague priors for baseline risk were specified in the time-to-event analyses, while in the SMR and proportion models, estimates of baseline risk were calculated from data for Zoledronic acid arms pooled across studies. Some data were missing. Where hazard ratios were not reported or derivable in the primary study, Kaplan-Meier estimates and numbers at risk (if available) were used, applying the methods of Tierney,[70] to estimate the hazard ratio. Mean imputation was used where there was missing data (e.g. standard deviations) in the analysis of skeletal morbidity rates.	Tierney[70] to estimate the hazard ratio. Pairwise hazard ratios were estimated from the median of the posterior distribution with credible intervals taken from the 2.5% and 97.5% percentiles. ~~The analyses included very few trials, so confidence intervals were bootstrapped to address the small amount of data. The same approach was taken for modelling rate ratios in the analysis of time to first and subsequent SREs.~~ Ten thousand MCMC simulations were used in the analysis following a burn-in of 10,000. The same approach was taken for modelling rate ratios in the analysis of time to first and subsequent SREs. For SMR and proportions of patients with an SRE, random effects models were ~~also used.~~ adopted using arm-based data. The data included in the SMR models were mean SMR and standard deviation along with the number of patients. Where standard deviations were not reported, values were imputed by taking the mean of reported SDs from other studies but for the same treatment. The robustness of the imputation was tested by comparing results with those obtained by treating missing data as an uncertain parameter. For the proportions with an SRE, the numbers of patients and the numbers with an SRE were used. ~~In the SMR and proportion models, median estimates were taken from 10,000 MCMC simulations after a burn-in of 10,000, with lower and upper 95% confidence limits taken from 2.5% and 97.5% percentiles respectively.~~ Posterior distributions for relative treatment effects were estimated from the absolute risks of outcome from the relevant individual treatments. Median estimates and credible intervals were taken from 10,000 MCMC simulations after a burn-in of 10,000. In order to estimate the absolute risk of outcome in the analyses of arm-based data, it was necessary to include an estimate of the baseline risk of the control treatment in the models. Zoledronic acid was treated as the ~~baseline comparator~~ reference treatment in each analysis as it is the treatment common to the largest number of trials and is present in multiple included studies for each NMA. ~~Vague priors for baseline risk were specified in the time-to-event analyses, while in the SMR and proportion models, estimates of baseline risk were calculated from data for Zoledronic acid arms pooled across studies~~. Single-arm meta-analyses of zoledronic acid were conducted to estimate baseline risk, from studies included in the NMA that had zoledronic acid as one of its comparators. The data in the time-to-event analyses, however, were

			trial-based and baseline risk could not be estimated so the absolute effect of the reference treatment was set to zero in these models. ~~Some data were missing. Where hazard ratios were not reported or derivable in the primary study, Kaplan-Meier estimates and numbers at risk (if available) were used, applying the methods of Tierney,[70] to estimate the hazard ratio. Mean imputation was used where there was missing data (e.g. standard deviations) in the analysis of skeletal morbidity rates.~~ The quality of the models was examined by inspecting convergence using Gelman-Rubin-Brooks plots, assessing autocorrelation between iterations of the Markov chain and checking whether the MC error was less than 5% of the posterior standard deviation.
62	6.2.10 Table 17		Replace with Table 17 above
63	6.2.10	In the AG NMA the difference was statistically significant, [redacted]. The indirect result for denosumab versus zoledronic acid is different from the direct result because within a NMA baseline risk of zoledronic acid is changed because of the other studies included.	In the AG NMA the difference was statistically significant, [redacted] for denosumab versus zoledronic acid and denosumab versus placebo, [redacted]. ~~The indirect result for denosumab versus zoledronic acid is different from the direct result because within a NMA baseline risk of zoledronic acid is changed because of the other studies included.~~
63	6.2.10 Table 18		Replace with Table 18 above
67	6.3	The results from the AG NMA show that denosumab compared with zoledronic acid, placebo or pamidronate significantly delayed the time to first SRE and significantly reduced the risk of first-and-subsequent SRE.	The results from the AG NMA show that denosumab compared with zoledronic acid or placebo~~, or pamidronate~~ significantly delayed the time to first SRE. For these comparisons and denosumab versus pamidronate, denosumab significantly reduced the risk of first-and-subsequent SREs.
84	7.2.10 Table 33		Replace with Table 33 above
85	7.2.10 Table 34		Replace with Table 34 above
96	8.2.10	The NMA results were statistically significant in favour of denosumab compared with zoledronic acid or placebo for time to first on-study SRE.	~~The NMA results were statistically significant in favour of denosumab compared with zoledronic acid or placebo for time to first on-study SRE~~. The NMA results favoured denosumab compared with zoledronic acid or placebo for time to first on-study SRE but were not statistically significant.
96	8.2.10 Table 40		Replace with Table 40 above
96	8.2.10 Table 41		Replace with Table 41 above

102	9.2.10 Table 43		Replace with Table 43 above
102	9.2.10 Table 44		Replace with Table 44 above
102	9.2.10	There was a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for this outcome.	There was a statistically significant difference in favour of denosumab compared with ~~zoledronic acid or~~ placebo for this outcome.
103	9.3	In the AG NMA, there was a statistically significant difference in favour of denosumab compared with placebo for time to first on-study SRE and risk of developing first-and-subsequent SREs, …	In the AG NMA, there was a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for time to first on-study SRE and compared with placebo for risk of developing first-and-subsequent SREs, …
118	10.2.10 Table 55		Replace with Table 55 above
118	10.2.10	The AG NMA results were statistically significant in favour of denosumab compared with zoledronic acid or placebo. [redacted]	The AG NMA results were statistically significant in favour of denosumab compared with ~~zoledronic acid or~~ placebo while the result for the comparison with zoledronic acid was not statistically significant, although the direction of effect favoured denosumab. [redacted]
119	10.2.10 Table 56		Replace with Table 56 above
220	13.1.1	In the Assessment Group's NMA, there was a statistically significant difference in favour of denosumab compared with zoledronic acid, pamidronate or placebo for both time to first on-study SRE and risk of first-and subsequent SREs (Table 120).	In the Assessment Group's NMA, there was a statistically significant difference in favour of denosumab compared with zoledronic acid~~,~~ ~~pamidronate~~ or placebo for ~~both~~ time to first on-study SRE and for these comparisons plus denosumab versus pamidronate for risk of first- and subsequent SREs (Table 120).
222	13.1.1	In the Assessment Group's NMA, there was a statistically significant difference in favour of denosumab compared with placebo for both time to first on-study SRE and risk of first-and-subsequent SREs. In the comparison with zoledronic acid there was a statistically significant difference in favour of denosumab for time to first on-study SRE but not for risk of first-and-subsequent SREs, although the direction of effect favoured denosumab (Table 120).	In the Assessment Group's NMA, ~~there was a statistically significant difference in favour of~~ the direction of effect of the comparisons of denosumab compared with zoledronic acid or placebo ~~favoured denosumab~~ for both time to first on-study SRE and risk of first-and-subsequent SREs but only the comparison with placebo for risk of first-and-subsequent SRE was statistically significant (Table 120). ~~In the comparison with zoledronic acid there was a statistically significant difference in favour of denosumab for time to first on-study SRE but not for risk of first-and-subsequent SREs, although the direction of effect favoured denosumab (Table 120).~~
222	13.1.1	In the Assessment Group's NMA there was a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for both time to first on-study SRE and	In the Assessment Group's NMA there was a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for ~~both~~ time to first on-study SRE and

		risk of first-and subsequent on-study SREs (Table 120).	compared with placebo for risk of first-and subsequent on-study SREs (Table 120).
223	13.1.1	The Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for both time to first on-study SRE and risk of first-and subsequent SREs, [redacted] (Table 120).	The Assessment Group's NMA reported a statistically significant difference in favour of denosumab compared with zoledronic acid or placebo for ~~both~~ time to first on-study SRE and compared with placebo for risk of first-and subsequent SREs, [redacted] (Table 120).
225	13.1.1 Table 120		Update with revised AG NMA data contained in Tables 17, 18, 33, 34, 40, 41, 43, 44, 55 and 56 above.
227	13.1.3	There were primary studies (other than those comparing denosumab) which did not report complete results, so some treatment effects used in the NMA (including levels of precision of the effects) were estimated and therefore subject to uncertainty despite the robust estimation methods employed. The small number of trials in each of the NMAs add to the uncertainty in the results, particularly as some of the individuals trials were small themselves and there were no instances (for any comparison between two treatments within an NMA) where there was sufficient comparable direct evidence to include more than one trial. This small amount of data resulted in wide ranges of parameter estimates at the extremes of the posterior distributions due to possible errors in simulation, despite convergent models. The estimates of treatment for the time-dependent outcomes were therefore presented with bootstrapped confidence intervals to address this consequence from the small amount of data, although in this context it resulted in narrower confidence intervals which should be interpreted accordingly.	There were primary studies (other than those comparing denosumab) which did not report complete results, so some treatment effects used in the NMA (including levels of precision of the effects) were estimated and therefore subject to uncertainty, although when missing data were treated as uncertain parameters the impact on the results was negligible ~~despite the robust estimation methods employed~~. The small number of trials in each of the NMAs add to the uncertainty in the results, particularly as some of the individuals trials were small themselves and there were no instances (for any comparison between two treatments within an NMA) where there was sufficient comparable direct evidence to include more than one trial. ~~This small amount of data resulted in wide ranges of parameter estimates at the extremes of the posterior distributions due to possible errors in simulation, despite convergent models. The estimates of treatment for the time-dependent outcomes were therefore presented with bootstrapped confidence intervals to address this consequence from the small amount of data, although in this context it resulted in narrower confidence intervals which should be interpreted accordingly.~~
235	14.1	In both the Assessment Group's network meta-analysis, there was a statistically significant difference in favour of denosumab for both time to first SRE and risk of first-and subsequent SRE, [redacted].	In ~~both~~ the Assessment Group's network meta-analysis, there was a statistically significant difference in favour of denosumab for both time to first SRE and risk of first-and subsequent SRE for most comparisons, [redacted].

Economics errata

Page number	Section/ Table	Text in AR	Correction
xxiv- xxvi	2	For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around 0.013 QALYs. This is again small, and does not justify the additional cost of £1,691 per patient compared to zoledronic acid. With the PAS [redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is £158,844 per QALY. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has little impact upon the results, as these estimates are reasonably close to the pooled all patient estimates. For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.020 QALY while compared to BSC it is 0.030 QALYs, at net costs without the PAS of £941 and £3,880 respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £46,976 per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at £35,732 per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £167,503 per QALY. This may arise in large part due to the estimated step change in HRQoL arising from a patient's first SRE. "Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around £100 result in cost effectiveness estimates of between £11,800 per QALY and £13,900 per QALY. The impact of applying the SRE subgroup specific estimates within this group is quite large. While it improves the estimates cost effectiveness of denosumab compared to BSC for SRE naïve patients, even with the PAS it is not sufficient to render it cost effective. Due to the SRE experienced relative risk for SREs being only [redacted] compared to zoledronic acid, the cost	For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around ~~0.013~~ 0.007 QALYs. This is again small, and does not justify the additional cost of £1707 ~~£1,691~~ per patient compared to zoledronic acid. With the PAS [redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is £157,829 ~~£158,844~~ per QALY. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has little impact upon the results, as these estimates are reasonably close to the pooled all patient estimates. For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.009 ~~0.020~~ QALY while compared to BSC it is 0.035 ~~0.030~~ QALYs, at net costs without the PAS of £1059 ~~£941~~ and £3951 ~~£3,880~~ respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £111,603 ~~£46,976~~ per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at ~~£35,732~~ £99,561 per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £170854 ~~£167,503~~ per QALY. This may arise in large part due to the estimated step change in HRQoL arising from a patient's first SRE. " And "Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around ~~£100~~ £50 result in cost effectiveness estimates of between ~~£11,800~~ £5,400 per QALY and £15,300

		effectiveness estimate for denosumab worsens to £38,458 per QALY compared to zoledronic acid among these patients. For lung cancer, possibly due to the short life expectancy, the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. Even with the PAS, the additional cost of £118 results in a cost effectiveness of £42,698 per QALY. ***Sensitivity analysis*** A concern within the modelling is BSC being assumed to have a zero incidence of the modelled SAEs. When the benefits from active treatments upon SREs are muted, there is the possibility that SAEs come to the fore and require a more detailed consideration. Sensitivity analyses that completely exclude SAEs from the analysis do improve the cost effectiveness of denosumab compared to BSC, but this in itself is not sufficient to render denosumab cost effective. Even with the PAS, all but one of the cost effectiveness estimates remain above £50k per QALY with a large majority being above £100k per QALY. The exception is the cost effectiveness estimate for SRE naïve prostate cancer patients, which within the pooled clinical effectiveness estimates analysis sees denosumab have a cost effectiveness estimate compared to BSC of £47,533 per QALY when all SAEs are excluded from the analysis." And "The other aspect that may have an impact is the treatment of spinal cord compressions. Extending the average quality of life decrement measured in the five months subsequent to the compression through to death improves the estimated cost effectiveness, particularly among SRE naïve prostate cancer patients. This has to be read in conjunction with the above comment on the change in utility estimated between SRE naïve patients and SRE experienced patients. But this average decrement being applied through to death improves the cost effectiveness of denosumab among SRE naïve prostate cancer patients from £69,510 per QALY to £51,655 per QALY compared to BSC. Applying the maximum decrement rather than the average further improves it to £43,905 per QALY. But applying these within the analyses that also apply the SRE subgroup specific hazards only improves it to £81,273 per QALY for the average decrement and to £67,508 per QALY for the maximum	~~£13,900~~ per QALY. The impact of applying the SRE subgroup specific estimates within this group is quite large. While it improves the estimates cost effectiveness of denosumab compared to BSC for SRE naïve patients, even with the PAS it is not sufficient to render it cost effective. Due to the SRE experienced relative risk for SREs being only [redacted] compared to zoledronic acid, the cost effectiveness estimate for denosumab worsens dramatically to £155,285 ~~ to £38,458~~ per QALY compared to zoledronic acid among these patients. For lung cancer, possibly due to the short life expectancy, the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. ~~Even with~~ With the PAS, the additional cost of ~~£118~~ £43 results in a cost effectiveness of £12,743 ~~£42,698~~ per QALY. ***Sensitivity analysis*** A concern within the modelling is BSC being assumed to have a zero incidence of the modelled SAEs. When the benefits from active treatments upon SREs are muted, there is the possibility that SAEs come to the fore and require a more detailed consideration. Sensitivity analyses that completely exclude SAEs from the analysis do improve the cost effectiveness of denosumab compared to BSC, but this in itself is not sufficient to render denosumab cost effective. Even with the PAS, all but one of the cost effectiveness estimates remain above £50k per QALY with a large majority being above £100k per QALY. ~~The exception is the cost effectiveness estimate for SRE naïve prostate cancer patients, which within the pooled clinical effectiveness estimates analysis sees denosumab have a cost effectiveness estimate compared to BSC of £47,533 per QALY when all SAEs are excluded from the analysis."~~ And "The other aspect that may have an impact is the treatment of spinal cord compressions. Extending the average quality of life decrement measured in the five months subsequent to the compression through to death improves the estimated cost effectiveness,

		decrement. There is limited data on the rates of paralysis from spinal cord compression and the cost estimates from averaging reference costs may be too low. CG75 suggests an average therapy cost of £14,173 [£13,705]. Adding this to the average rehabilitation costs and applying the average decrement through to death results in a cost effectiveness estimate for SRE naïve prostate patients of [redacted] per QALY compared to BSC, and [redacted] per QALY for the maximum decrement. But within the analyses that apply the SRE subgroup specific hazards the estimates rise to [redacted] per QALY and [redacted] respectively.	particularly among SRE naïve prostate cancer patients. This has to be read in conjunction with the above comment on the change in utility estimated between SRE naïve patients and SRE experienced patients. But this average decrement being applied through to death improves the cost effectiveness of denosumab among SRE naïve prostate cancer patients with the PAS from £72,269 ~~£69,510~~ per QALY to £56,420 ~~£51,655~~ per QALY compared to BSC. Applying the maximum decrement rather than the average further improves it to £49,032 ~~£43,905~~ per QALY. ~~But applying these within the analyses that also apply the SRE subgroup specific hazards only improves it to £81,273 per QALY for the average decrement and to £67,508 per QALY for the maximum decrement.~~ There is limited data on the rates of paralysis from spinal cord compression and the cost estimates from averaging reference costs may be too low. CG75 suggests an average therapy cost of £14,173 [£13,705]. Adding this to the average rehabilitation costs and applying the average decrement through to death results in a cost effectiveness estimate for SRE naïve prostate patients of [redacted] per QALY compared to BSC, and [redacted] per QALY for the maximum decrement. ~~But within the analyses that apply the SRE subgroup specific hazards the estimates rise to [redacted] per QALY and [redacted] respectively~~."
183-184	Table 101	"Excluding ONJ and renal toxicity utility impact beyond trial average" And "No SAE P1+"	"~~Excluding~~ ONJ and renal toxicity utility impact beyond trial average duration to average cohort survival" And "~~No~~ SAE P1+"
184	11.3.1	"In addition to these, given the zoledronic acid is shortly coming off patent the impact of a range of reductions in the price of zoledronic acid are also reported."	"In addition to these, given that ~~the~~ zoledronic acid is shortly coming off patent the impact of a range of reductions in the price of zoledronic acid are also reported."
189	11.3.2 Table 106		Replace with Table 106 below
189-190	11.3.2	"The net gain from denosumab over zoledronic acid of 0.013 QALYs is actually somewhat higher than that estimated by the manufacturer. This may be due to the treatment of utilities during the first five months of the modelling. But this remains a relatively small gain, which without the	"The net gain from denosumab over zoledronic acid of ~~0.013~~ 0.007 QALYs is ~~actually somewhat higher than~~ in line with that estimated by the manufacturer. ~~This may be due to the treatment of utilities during the first five months of the~~

		PAS requires an additional £1,680 resulting in a cost effectiveness of £126,821 per QALY. For those contraindicated to bisphosphonates the cost effectiveness of denosumab compared to BSC is worse. Patient gains are larger at 0.027 QALYs but the net cost rises by a greater amount to £6,114 resulting in a cost effectiveness estimate of £224,411 per QALY. With the PAS, the anticipated cost savings are less than anticipated by the manufacturer but this appears to be broadly in line with the assumed costs of SREs and SAEs. Given the cost saving and the anticipated patient gains, denosumab is estimated to dominate zoledronic acid. Probabilistic modelling over 2,000 iterations is broadly in line with this, estimating the same 0.013 QALYs, but a slightly smaller average cost saving of £267. For those contraindicated to bisphosphonates, the cost effectiveness of denosumab compared to BSC is again considerably worse, with a central estimate across all these patients of £152,847 per QALY. Across all patients the probabilistic modelling suggests similar central estimates of 0.027 QALYs and a net cost of £4,163 to yield a cost effectiveness estimate of £151,778 per QALY."	~~modelling.~~ But this remains a relatively small gain, which without the PAS requires an additional ~~£1,680~~ £1,707 resulting in a cost effectiveness of ~~£126,821~~ £245,264 per QALY. For those contraindicated to bisphosphonates the cost effectiveness of denosumab compared to BSC is broadly similar ~~worse~~. Patient gains are larger at 0.027 QALYs but the net cost rises by a ~~greater~~ similar amount to ~~£6,114~~ £6,242 resulting in a cost effectiveness estimate of ~~£224,411~~ £229,547 per QALY. With the PAS, the anticipated cost savings are less than anticipated by the manufacturer but this appears to be broadly in line with the assumed costs of SREs and SAEs. Given the cost saving and the anticipated patient gains, denosumab is estimated to dominate zoledronic acid. Probabilistic modelling over 2,000 iterations is broadly in line with this, estimating the same ~~0.013~~ 0.007 QALYs, but a slightly smaller average cost saving of ~~£267~~ £243. For those contraindicated to bisphosphonates, the cost effectiveness of denosumab compared to BSC is again considerably worse, with a central estimate across all these patients of ~~£152,847~~ £157,829 per QALY. Across all patients the probabilistic modelling suggests similar central estimates of ~~0.027~~ 0.028 QALYs and a net cost of ~~£4,163~~ £4,269 to yield a cost effectiveness estimate of ~~£151,778~~ £154,944 per QALY."
190	11.3.2 Figure 13		Replace with Figure 13 below
191	Table 107		Replace with Table 107 below
191-192	11.3.2	The main sensitivity of results is around the SAEs and the discontinuation rates. Given the higher rate of renal failure within the zoledronic acid arm removing the assumed ongoing utility decrement associated with this and ONJ reduces the anticipated benefits from denosumab by around a third to up to one half, with a parallel adverse impact upon the cost effectiveness estimate. Excluding discontinuations also has quite a large impact, though the increase in the net patient gains is broadly mirrored by an increase in the net cost resulting in a relatively static ICER.	The main sensitivity of results is around the SAEs and the discontinuation rates. Given the higher rate of renal failure within the zoledronic acid arm ~~removing the assumed ongoing utility decrement associated with this and ONJ reduces~~ assuming this last for longer than that measured in the trial affects results. If SAE ONJ and renal failure last on average for the average remaining cohort survival the anticipated benefits from denosumab over zoledronic acid increase by ~~around a third to~~ up to one half, with a parallel ~~adverse~~

		A reduction in the price of zoledronic acid of 10% results in the cost effectiveness of denosumab compared to zoledronic acid across all breast cancer patients including the PAS [redacted].	impact upon the cost effectiveness estimate. Excluding discontinuations also has quite a large impact when compared to BSC, though the increase in the net patient gains is broadly mirrored by an increase in the net cost resulting in a relatively static ICER. A reduction in the price of zoledronic acid of between [redacted] and [redacted] is sufficient to result~~s~~ in the cost effectiveness of denosumab compared to zoledronic acid across all breast cancer patients including the PAS worsening to levels which might not be considered cost effective. ~~worsening to £8,239 per QALY, while a reduction of 20% results in a cost effectiveness of £36,874 per QALY with this continuing linearly thereafter.~~
192	11.3.2 Table 108		Replace with Table 108 below
193	11.3.2 Table 109		Replace with Table 109 below
193-194	11.3.2	"Without the PAS, the relatively small patient gain of 0.020 QALYs at an additional cost of £941 results in a cost effectiveness compared to zoledronic acid of £46,976 per QALY. But with the PAS, cost savings and dominance over zoledronic acid are anticipated. The cost effectiveness is estimated to be slightly worse among the SRE experienced than across the patient group as a whole, though this may be due in part to the step change in HRQoL that is applied when SRE naïve patients experience their first SRE. But with the PAS, cost savings are again anticipated which again results in dominance over zoledronic acid. The probabilistic modelling suggests central estimates of a gain of 0.020 QALYs and a cost saving of £244 across all patients. For those contraindicated to bisphosphonates, even with the PAS the cost effectiveness of denosumab compared to BSC is poor at between £70k per QALY and £405k per QALY. Across all patients the probabilistic modelling suggests similar central estimates of 0.030 QALYs and a net cost of £2,694 to yield a cost effectiveness estimate of £90,067 per QALY."	"Without the PAS, the relatively small patient gain of 0.0~~20~~09 QALYs at an additional cost of £~~941~~1059 results in a cost effectiveness compared to zoledronic acid of £~~46,976~~ 111,603 per QALY. But with the PAS, cost savings and dominance over zoledronic acid are anticipated. The cost effectiveness is estimated to be slightly worse among the SRE experienced than across the patient group as a whole, though this may be due in part to the step change in HRQoL that is applied when SRE naïve patients experience their first SRE. But with the PAS, cost savings are again anticipated which again results in dominance over zoledronic acid. The probabilistic modelling suggests central estimates of a gain of 0.0~~20~~09 QALYs and a cost saving of £~~244~~123 across all patients. For those contraindicated to bisphosphonates, even with the PAS the cost effectiveness of denosumab compared to BSC is poor at between £70k per QALY and ~~£405k~~ £240k per QALY. Across all patients the probabilistic modelling suggests similar central estimates of 0.03~~0~~5 QALYs and a net cost of £2,~~694~~764 to yield a cost effectiveness estimate of £~~90,067~~ 78,756 per QALY."

194	11.3.2 Figure 14		Replace with Figure 14 below
196	11.3.2 Table 110		Replace with Table 110 below
197-198	11.3.2	"One of the main sensitivities relates to the application of the manufacturer NMA results which halves the patient benefits associated with denosumab. This is as would be expected given the HR for the time to first SRE of 0.82 compared to the assessment group network meta-analysis estimate of 0.57. Note that this only affects the SRE naïve patients. The relative risks for subsequent SREs are more in line at [redacted] for the manufacturer and 0.83 for the assessment group NMA and as a consequence there is little impact among SRE experienced patients." And "If the average (or maximum) spinal cord compression utility decrement is carried forward in the modelling for SRE naïve prostate patients this yield a cost effectiveness estimate for denosumab with the PAS compared to BSC of £51,655 per QALY (or £43,905 per QALY). There is limited data on the rates of paralysis from spinal cord compression and the cost estimates from averaging reference costs may be too low. CG75 suggests an average therapy cost of £14,173 [£13,705]. Adding this to the average rehabilitation costs and applying the average spinal cord compression decrement through to death results in a cost effectiveness estimate for the with PAS analysis for SRE naïve prostate patients of [redacted] per QALY compared to BSC, and [redacted] per QALY when applying the maximum decrement. But within the analyses that apply the SRE subgroup specific hazards these estimates rise to [redacted] per QALY and [redacted] respectively." And "A concern within the modelling is BSC being assumed to have a zero incidence of the modelled SAEs. When the benefits from active treatments upon SREs are muted, there is the possibility that SAEs come to the fore and require a more detailed consideration. Sensitivity analyses that completely exclude SAEs from the analysis do improve the cost effectiveness of denosumab compared to BSC, but this in itself is not sufficient to render denosumab cost effective. Even with the PAS, all but one of the cost effectiveness estimates remain above £50k per QALY with a large majority being above	~~"One of the main sensitivities relates to the application of the manufacturer NMA results which halves the patient benefits associated with denosumab. This is as would be expected given the HR for the time to first SRE of 0.82 compared to the assessment group network meta-analysis estimate of 0.57. Note that this only affects the SRE naïve patients. The relative risks for subsequent SREs are more in line at [redacted] for the manufacturer and 0.83 for the assessment group NMA and as a consequence there is little impact among SRE experienced patients."~~ And "If the average (or maximum) spinal cord compression utility decrement is carried forward in the modelling for SRE naïve prostate patients this yield a cost effectiveness estimate for denosumab with the PAS compared to BSC of ~~£51,655~~ £56,420 per QALY (or ~~£43,905~~ £49,032 per QALY). There is limited data on the rates of paralysis from spinal cord compression and the cost estimates from averaging reference costs may be too low. CG75 suggests an average therapy cost of £14,173 [£13,705]. Adding this to the average rehabilitation costs and applying the average spinal cord compression decrement through to death results in a cost effectiveness estimate for the with PAS analysis for SRE naïve prostate patients of [redacted] per QALY compared to BSC, and [redacted] per QALY when applying the maximum decrement. ~~But within the analyses that apply the SRE subgroup specific hazards these estimates rise to [redacted] per QALY and [redacted] respectively.~~" And "~~A concern within the modelling is BSC being assumed to have a zero incidence of the modelled SAEs. When the benefits from active treatments upon SREs are muted, there is the possibility that SAEs come to the fore and require a more detailed consideration. Sensitivity analyses~~

		£100k per QALY. The exception is the cost effectiveness estimate for SRE naïve prostate cancer patients, which within the pooled clinical effectiveness estimates analysis sees denosumab have a cost effectiveness estimate compared to BSC of £47,533 per QALY when all SAEs are excluded from the analysis." And "A reduction in the price of zoledronic acid of 10% results in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced prostate cancer patients including the PAS [redacted]."	~~that completely exclude SAEs from the analysis do improve the cost effectiveness of denosumab compared to BSC, but this in itself is not sufficient to render denosumab cost effective. Even with the PAS, all but one of the cost effectiveness estimates remain above £50k per QALY with a large majority being above £100k per QALY. The exception is the cost effectiveness estimate for SRE naïve prostate cancer patients, which within the pooled clinical effectiveness estimates analysis sees denosumab have a cost effectiveness estimate compared to BSC of £47,533 per QALY when all SAEs are excluded from the analysis~~." And A reduction in the price of zoledronic acid of between [redacted] and [redacted] is sufficient to result~~s~~ in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced prostate cancer patients including the PAS worsening to levels which might not be considered cost effective. ~~worsening to £17,337 per QALY, while a reduction of 20% results in a cost effectiveness of £54,150 per QALY with this continuing linearly thereafter~~."~~~~
198	11.3.2 Table 111		Replace with Table 111 below
199	11.3.2 Table 112		Replace with Table 112 below
200	11.3.2	"For other solid tumours including lung, possibly due to around 40% having lung cancer with the associated poor survival, the additional patient benefits from denosumab over zoledronic acid are muted: between 0.007 QALYs for SRE experienced patients and 0.008 QALYs for SRE naive patients. Without the PAS the additional cost of around £880 results in cost effectiveness estimates of more than £100k per QALY. [redacted] This results in an additional average cost of around £100 and cost effectiveness estimates of between £11,800 per QALY and £13,900 per QALY. Probabilistic modelling is again in line with this, an average gain of 0.008 QALYs at an additional average cost of £101 resulting in a central estimate of £13,200 per QALY across all patients. As would be anticipated given the	"For other solid tumours including lung, possibly due to around 40% having lung cancer with the associated poor survival, the additional patient benefits from denosumab over zoledronic acid are muted: between ~~0.007~~ 0.004 QALYs for SRE experienced patients and 0.008 QALYs for SRE naive patients. Without the PAS the additional cost of around £840 ~~£880~~ results in cost effectiveness estimates of more than £100k per QALY. [redacted] This results in an additional average cost of around ~~£100~~ £50 and cost effectiveness estimates of between £5,400 ~~£11,800~~ per QALY and £15,300 ~~£13,900~~ per QALY. Probabilistic modelling is again in line with this, an average gain of 0.006

		preceding analysis, for those contraindicated to bisphosphonates, even with the PAS denosumab is not estimated to be cost effective against BSC. Across all patients the probabilistic modelling suggests similar central estimates of 0.013 QALYs and a net cost of £1,791 to yield a cost effectiveness estimate of £134,912 per QALY compared to BSC. Note the apparently perverse impact among SRE experienced patients, in that denosumab is estimated to result in a smaller gain against BSC than against zoledronic acid. This is likely to have arisen from BSC being assumed not to be associated with any SAEs. This may be a reasonable approximation when there are clear differences in SRE rates between BSC and the active treatments. But it may not be so reasonable when differences are very small, and SAEs may come more to the fore. "	~~0.008~~ QALYs at an additional average cost of £56 ~~£101~~ resulting in a central estimate of £9,391 ~~£13,200~~ per QALY across all patients. As would be anticipated given the preceding analysis, for those contraindicated to bisphosphonates, even with the PAS denosumab is not estimated to be cost effective against BSC. Across all patients the probabilistic modelling suggests similar central estimates of 0.017 ~~0.013~~ QALYs and a net cost of £1,771 ~~£1,791~~ to yield a cost effectiveness estimate of £102,102 ~~£134,912~~ per QALY compared to BSC. ~~Note the apparently perverse impact among SRE experienced patients, in that denosumab is estimated to result in a smaller gain against BSC than against zoledronic acid. This is likely to have arisen from BSC being assumed not to be associated with any SAEs. This may be a reasonable approximation when there are clear differences in SRE rates between BSC and the active treatments. But it may not be so reasonable when differences are very small, and SAEs may come more to the fore.~~ "
201	11.3.2 Figure 15		Replace with Figure 15 below
202	11.3.2 Table 113		Replace with Table 113 below
203	11.3.2	"In the above, the main sensitivities are to the source of the clinical effectiveness data and the treatment of SAEs and discontinuations. The manufacturer NMA increases the anticipated benefits within the all patient modelling by up to around 20%, with this mainly occurring among SRE naïve patients. Again, this is not unanticipated given the assessment group estimate for the HR for time to first SRE of 0.93 as compared to [redacted] from the manufacturer. The relative risk estimates for subsequent SREs are more similar at 0.87 and [redacted] respectively, and as a consequence the impact upon SRE patients is less." And "While small in absolute terms, excluding SAEs has a reasonable percentage impact upon the anticipated patient gain compared to zoledronic acid and the ICER worsens considerably as a result. Partly as a consequence of this, removing discontinuations increases the modelled patient	~~"In the above, the main sensitivities are to the source of the clinical effectiveness data and the treatment of SAEs and discontinuations. The manufacturer NMA increases the anticipated benefits within the all patient modelling by up to around 20%, with this mainly occurring among SRE naïve patients. Again, this is not unanticipated given the assessment group estimate for the HR for time to first SRE of 0.93 as compared to [redacted] from the manufacturer. The relative risk estimates for subsequent SREs are more similar at 0.87 and [redacted] respectively, and as a consequence the impact upon SRE patients is less."~~ And ~~"While small in absolute terms, excluding SAEs has a reasonable percentage impact upon the anticipated patient gain compared to zoledronic acid and the ICER~~

		benefits though at some additional cost." And "A reduction in the price of zoledronic acid of 10% results in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced other solid tumours including lung cancer patients including the PAS [redacted]."	~~worsens considerably as a result. Partly as a consequence of this,~~ R~~r~~emoving discontinuations increases the modelled patient benefits though at some additional cost." And "A reduction in the price of zoledronic acid of [redacted] result~~s~~ in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced other solid tumours including lung cancer patients including the PAS worsening to levels which might not be considered cost effective [redacted]."
204	11.3.2 Table 114		Replace with Table 114 below
204	11.3.2	"The SRE subgroup specific clinical effectiveness estimates have the most dramatic impact upon this group of cancers. Possibly due to the short life expectancy and the limited time for an SRE naïve patient to experience their first SRE let alone their second, the better clinical effectiveness estimate for SRE naïve patients increases the estimated patient benefits by around 50% when compared to zoledronic acid. With the PAS this results in a cost effectiveness of only £4,076 per QALY, but unfortunately for this patient group the cost effectiveness against BSC remains poor: £69,766 per QALY. The effectiveness estimate for the SRE experienced sub-group is that denosumab is not much better than zoledronic acid, and even with the PAS the cost effectiveness estimate worsens to £38,458 per QALY."	"The SRE subgroup specific clinical effectiveness estimates have the most dramatic impact upon this group of cancers. ~~Possibly due to the short life expectancy and the limited time for an SRE naïve patient to experience their first SRE let alone their second, the better clinical effectiveness estimate for SRE naïve patients increases the estimated patient benefits by around 50% when compared to zoledronic acid. With the PAS this results in a cost effectiveness of only £4,076 per QALY, but unfortunately for this patient group the cost effectiveness against BSC remains poor: £69,766 per QALY. The effectiveness estimate for the SRE experienced sub-group is that denosumab is not much better than zoledronic acid, and even with the PAS the cost effectiveness estimate worsens to £38,458 per QALY.~~ As would be anticipated, given the RR among the SRE experienced their modelled benefits from denosumab over zoledronic acid are very slight and do not justify the additional cost.
205	11.3.2 Table 115		Replace with Table 115 below
205	11.3.2	"The results for lung cancer are broadly similar to the previous analysis. For the comparison with	"The results for lung cancer are broadly similar to the previous analysis. For the

		zoledronic acid patient benefits are muted among SRE experienced patients: 0.003 QALYs. This may be a factor of their short life expectancy, but with the PAS the additional costs of £118 result in a cost effectiveness estimate of £42,698. The reverse applies to the SRE naïve subgroup where larger gains of 0.009 QALYs are achieved at minimal additional cost once the PAS is included. But the cost effectiveness for these patients compared to BSC remains poor at an estimated £139,364 per QALY. As for the other analyses, the probabilistic modelling central estimates are broadly in line with those of the deterministic analysis. Across all patients the central estimate is of a 0.006 QALY gain compared to zoledronic acid and a 0.009 QALY gain compared to BSC. This is at an additional net cost central estimate of £1,640 and £61 with the PAS respectively."	comparison with zoledronic acid patient benefits are muted among SRE experienced patients: 0.003 QALYs. This may be a factor of their short life expectancy, but with the PAS the additional costs of ~~£118~~ 43 result in a cost effectiveness estimate of £12,742 ~~42,698~~. ~~The reverse~~ This also applies to the SRE naïve subgroup where larger gains of 0.00~~6~~9 QALYs are achieved at minimal additional cost once the PAS is included. But the cost effectiveness for these patients compared to BSC remains poor at an estimated ~~£139,364~~ £110,671 per QALY. As for the other analyses, the probabilistic modelling central estimates are broadly in line with those of the deterministic analysis. Across all patients the central estimate is of a 0.00~~5~~6 QALY gain compared to zoledronic acid and a 0.012~~09~~ QALY gain compared to BSC. This is at an additional net cost central estimate of £32 ~~£1,640~~ and £1582 ~~£61~~ with the PAS respectively."
206	11.3.2 Figure 16		Replace with figure 16 below
207	11.3.2 Table 116		Replace with Table 116 below
208	11.3.2	"For the comparison with zoledronic acid among SRE experienced patients, the number of SREs avoided and the patient gains anticipated by the base case are extremely muted. Given the relative risk for subsequent SREs of 0.97 as estimated within the AG NMA it appears that results within among SRE experienced patients may be being driven at least in part by the rates of SAEs. The sensitivity analyses for lung cancer that remove the discontinuations have a similar impact as within the OST+lung modelling, given that in the absence of other data the lung cancer modelling assumes the adverse event rates and discontinuations of the OST + lung modelling. Results are more predictable and stable among the SRE naïve patients, given the hazard ratio for time to first SRE among SRE naïve patients of 0.79 for denosumab compared to zoledronic acid and of 0.86 for zoledronic acid compared to placebo. The main sensitivities are in the treatment of utilities, with the removal of the step change going from naïve to experienced reducing patient benefits by around one third. Given the short life expectancy, the application of the van den Hout utility modifiers also has	"~~For the comparison with zoledronic acid among SRE experienced patients, the number of SREs avoided and the patient gains anticipated by the base case are extremely muted. Given the relative risk for subsequent SREs of 0.97 as estimated within the AG NMA it appears that results within among SRE experienced patients may be being driven at least in part by the rates of SAEs.~~ The sensitivity analyses for lung cancer that remove the discontinuations have a similar impact as within the OST+lung modelling, given that in the absence of other data the lung cancer modelling assumes the adverse event rates and discontinuations of the OST + lung modelling. ~~Results are more predictable and stable among the SRE naïve patients, given the hazard ratio for time to first SRE among SRE naïve patients of 0.79 for denosumab compared to zoledronic acid and of 0.86 for zoledronic acid compared to placebo.~~ The main sensitivities are in the treatment of utilities, with the removal of the step

		quite a large impact and also causes the patient benefits to be reduced by around one third. A reduction in the price of zoledronic acid of 10% results in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced other solid tumours including lung cancer patients including the PAS [redacted]."	change going from naïve to experienced reducing patient benefits by around one ~~third~~ quarter. Given the short life expectancy, the application of the van den Hout utility modifiers also has a reasonably large impact. ~~quite a large impact and also causes the patient benefits to be reduced by around one third~~. A reduction in the price of zoledronic acid of [redacted] result~~s~~ in the cost effectiveness of denosumab compared to zoledronic acid for SRE experienced other solid tumours including lung cancer patients including the PAS worsening to levels which might not be considered cost effective. [redacted]."
211-212	11.3.2 Table 117		Replace with Table 117 below
213-214	11.3.2 Table 118		Replace with Table 118 below
208	11.3.2	"Among the SRE experienced patients this sees the net impact of denosumab compared to zoledronic acid fall from a reduction in SREs of 0.290 to a reduction of only 0.088, with a parallel impact upon the anticipated patient benefits."	"Among the SRE experienced patients this sees the net impact of denosumab compared to zoledronic acid fall from a reduction in SREs of 0.135~~290~~ to a reduction of only 0.08~~8~~7, with a parallel impact upon the anticipated patient benefits."
209	11.3.2	"Within the modelling of other solid tumours including lung, the base case number of SREs avoided from denosumab compared to zoledronic acid for SRE experienced patients is reasonably sensitive to whether the assessment group NMA results are applied or the manufacturer NMA results. But whichever is applied the number of SREs avoided through use of denosumab over zoledronic acid is small and results become sensitive to the other parameters within the modelling, notable rates of SAEs and discontinuation rates."	"Within the modelling of other solid tumours including lung, ~~the base case number of SREs avoided from denosumab compared to zoledronic acid for SRE experienced patients is reasonably sensitive to whether the assessment group NMA results are applied or the manufacturer NMA results. But whichever is applied the number of SREs avoided through use of~~ denosumab over zoledronic acid is small and results become sensitive to the other parameters within the modelling, such as the treatment of ~~notable rates of~~ SAEs ~~and discontinuation rates~~."
209	11.3.2	"The above is further mirrored in the modelling of lung cancer, where the base case number of SREs avoided from denosumab compared to zoledronic acid for SRE experienced patients is very small given the relative risk of 0.97 for	"The OST plus NSCLC results are broadly ~~above is further~~ mirrored in the modelling of lung cancer~~, where the base case number of SREs avoided from denosumab compared to zoledronic acid for SRE~~

		subsequent SREs. In the light of the anticipated patient gains are small, and the cost effectiveness estimates are volatile to the input values for other model parameters such as SAEs and discontinuation rates. Results for denosumab compared to best supportive care are again more stable, and again this is particularly the case for SRE naïve patients for whom the relative risk for denosumab compared to zoledronic acid is 0.79 and for zoledronic acid compared to BSC is 0.86."	~~experienced patients is very small given the relative risk of 0.97 for subsequent SREs. In the light of the anticipated patient gains are small, and the cost effectiveness estimates are volatile to the input values for other model parameters such as SAEs and discontinuation rates. Results for denosumab compared to best supportive care are again more stable, and again this is particularly the case for SRE naïve patients for whom the relative risk for denosumab compared to zoledronic acid is 0.79 and for zoledronic acid compared to BSC is 0.86.~~"
216-217	11.3.2	For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around 0.013 QALYs. This is again small, and does not justify the additional cost of £1,691 per patient compared to zoledronic acid. With the PAS [redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is £158,844 per QALY. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has little impact upon the results, as these estimates are reasonably close to the pooled all patient estimates. For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.020 QALYs while compared to BSC it is 0.030 QALYs, at net costs without the PAS of £941 and £3,880 respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £46,976 per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at £35,732 per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £167,503 per QALY. This may arise in large part due to the estimated step change in HRQoL arising from a patient's first SRE. With the PAS, denosumab is estimated to be cost saving compared to zoledronic acid and so dominate it. For those contraindicated to bisphosphonates, denosumab is not estimated to be cost effective compared to BSC. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has a reasonably large impact upon the results. The	For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around 0.007 ~~0.013~~ QALYs. This is again small, and does not justify the additional cost of £1707 ~~£1,691~~ per patient compared to zoledronic acid. With the PAS [redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is £157,829 ~~£158,844~~ per QALY. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has little impact upon the results, as these estimates are reasonably close to the pooled all patient estimates. For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around ~~0.020~~ 0.009 QALYs while compared to BSC it is ~~0.030~~ 0.035 QALYs, at net costs without the PAS of £1059 ~~£941~~ and £3951 ~~£3,880~~ respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £111,603 ~~£46,976~~ per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at £99,561 ~~£35,732~~ per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £170,854 ~~£167,503~~ per QALY. This may arise in large part due to the estimated step change in HRQoL arising from a patient's first SRE. With the PAS, denosumab is estimated to be cost saving compared to zoledronic acid and so dominate it. For those contraindicated to bisphosphonates,

		impact of this on the modelling is not symmetric. As the model progresses, more patients fall into the SRE experienced group and as a consequence the estimated cost effectiveness of denosumab worsens. But the PAS is still sufficient for [redacted] denosumab being estimated to remain dominant over zoledronic acid. Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around £100 result in cost effectiveness estimates of between £11,800 per QALY and £13,900 per QALY. The impact of applying the SRE subgroup specific estimates within this group is quite large. While it improves the estimates cost effectiveness of denosumab compared to BSC for SRE naïve patients, even with the PAS it is not sufficient to render it cost effective. [redacted], the cost effectiveness estimate for denosumab worsens to £38,458 per QALY compared to zoledronic acid among these patients. For lung cancer, possibly due to the short life expectancy the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. Even with the PAS, the additional cost of £118 results in a cost effectiveness of £42,698 per QALY.	denosumab is not estimated to be cost effective compared to BSC. ~~Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has a reasonably large some impact upon the results. The impact of this on the modelling is not symmetric. As the model progresses, more patients fall into the SRE experienced group and as a consequence the estimated cost effectiveness of denosumab worsens. But the PAS is still sufficient for [redacted] denosumab being estimated to remain dominant over zoledronic acid~~. Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around ~~£100~~ £50 result in cost effectiveness estimates of between £5400~~11,800~~ per QALY and £15,300 ~~£13,900~~ per QALY. The impact of applying the SRE subgroup specific estimates within this group is quite large. While it improves the estimates cost effectiveness of denosumab compared to BSC for SRE naïve patients, even with the PAS it is not sufficient to render it cost effective. [redacted], the cost effectiveness estimate for denosumab worsens to £155,285 ~~£38,458~~ per QALY compared to zoledronic acid among these patients. For lung cancer, possibly due to the short life expectancy the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. ~~Even with~~ With the PAS, the additional cost of ~~£118~~ 43 results in a cost effectiveness of £12,743 ~~£42,698~~ per QALY.
232-233	13.2.1	"For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around 0.013 QALYs. This is again small, and does not justify the additional cost of £1,691 per patient compared to	"For the cost utility modelling within breast cancer, the lifetime gains across all patients are estimated to be around ~~0.013~~ 0.007 QALYs. This is again small, and does not justify the additional cost of ~~£1,691~~

		zoledronic acid. With the PAS [redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is £158,844 per QALY." And "For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.020 QALY while compared to BSC it is 0.030 QALYs, at net costs without the PAS of £941 and £3,880 respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £46,976 per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at £35,732 per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £167,503 per QALY. " And With the PAS, denosumab is estimated to be cost saving compared to zoledronic acid and so dominate it. For those contraindicated to bisphosphonates, denosumab is not estimated to be cost effective compared to BSC. Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has a reasonably large impact upon the results. But the PAS [redacted] resulting in denosumab being estimated to remain dominant over zoledronic acid. Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around £100 result in cost effectiveness estimates of between £11,800 per QALY and £13,900 per QALY. " And "For lung cancer, possibly due to the short life expectancy the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. Even with the PAS, the additional cost of £118 results in a cost effectiveness of £42,698 per QALY."	£1707 per patient compared to zoledronic acid. With the PAS [redacted] denosumab is estimated to dominate zoledronic acid. But for those contraindicated to bisphosphonates the cost effectiveness is poor: even with the PAS the cost effectiveness is ~~£158,844~~ £157,829 per QALY. " And "For the cost utility modelling within prostate cancer, across all patients the gain from denosumab over zoledronic acid is around 0.009 ~~0.020~~ QALY while compared to BSC it is 0.035 ~~0.030~~ QALYs, at net costs without the PAS of £1059 ~~£941~~ and £3951 ~~£3,880~~ respectively. Without the PAS, compared to zoledronic acid this results in a cost effectiveness of £111,603 ~~£46,976~~ per QALY. Cost effectiveness is estimated to be slightly better among the SRE naïve at ~~£35,732~~ £99,561 per QALY, but the quid pro quo is a worse cost effectiveness among the SRE experienced of £170854 ~~£167,503~~ per QALY." And With the PAS, denosumab is estimated to be cost saving compared to zoledronic acid and so dominate it. For those contraindicated to bisphosphonates, denosumab is not estimated to be cost effective compared to BSC. ~~Applying the SRE naïve and SRE experienced subgroup specific clinical effectiveness has a reasonably large impact upon the results. But the~~ The PAS [redacted] resulting in denosumab being estimated to remain dominant over zoledronic acid. Within the cost utility modelling of other solid tumours including lung, the gains from denosumab over zoledronic acid are estimated to be less than 0.01 QALYs. Without the PAS denosumab is not cost effective, but with it the small additional overall costs of around ~~£100~~ £50 result in cost effectiveness estimates of between ~~£11,800~~ £5,400 per QALY and £15,300

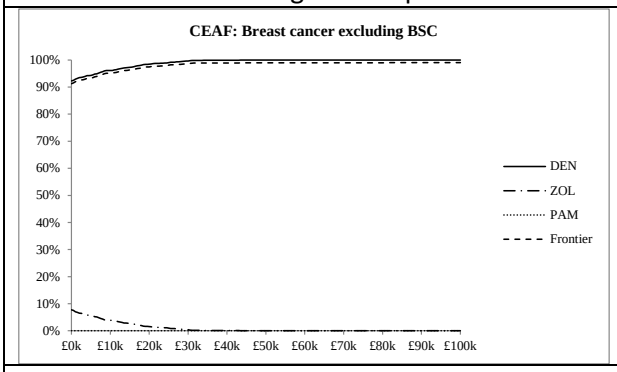
			~~£13,900~~ per QALY." And "For lung cancer, possibly due to the short life expectancy the patient gains from denosumab over zoledronic acid among SRE experienced patients are estimated to be small: 0.003 QALYs. ~~Even with~~ With the PAS, the additional cost of £43 ~~£118~~ results in a cost effectiveness of £12,743 ~~£42,698~~ per QALY."

Table 106 Breast cancer AG NMA cost effectiveness results

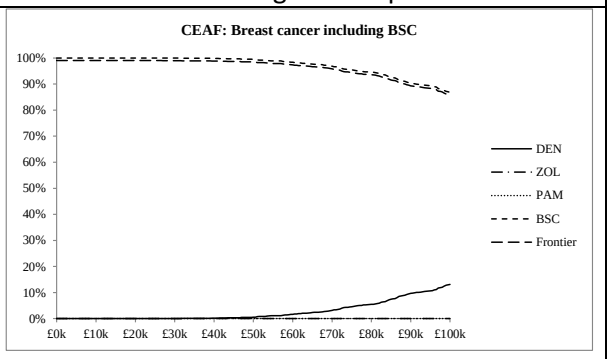
All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	3.159	-0.988	1.821	0.027				£6,242	£229,547
inc PAS								£4,292	£157,829
Zol. Acid	2.383	-0.211	1.841	0.007				£1,707	£245,264
inc PAS								-£243	Dominant
Denosumab	2.171		1.848						
inc PAS									
Pamidronate	2.445	-0.274	1.839	0.010				-£1,303	Dominant
inc PAS								-£3,253	Dominant
SRE Naive	SREs	net	QALYs	net				net	ICER
BSC	2.807	-0.962	1.850	0.035				£6,308	£181,092
inc PAS								£4,358	£125,109
Zol. Acid	2.031	-0.186	1.876	0.008				£1,747	£209,345
inc PAS								-£203	Dominant
Denosumab	1.845		1.884						
inc PAS									
Pamidronate	2.022	-0.177	1.875	0.009				-£1,168	Dominant
inc PAS								-£3,118	Dominant
SRE Exper	SREs	net	QALYs	net				net	ICER
BSC	3.667	-1.025	1.780	0.016				£6,146	£379,539
inc PAS								£4,196	£259,113
Zol. Acid	2.888	-0.247	1.791	0.005				£1,649	£332,185
inc PAS								-£301	Dominant
Denosumab	2.641		1.796						
inc PAS									
Pamidronate	3.055	-0.414	1.786	0.010				-£1,498	Dominant
inc PAS								-£3,448	Dominant

Figure 13 Breast cancer CEAFs including the PAS

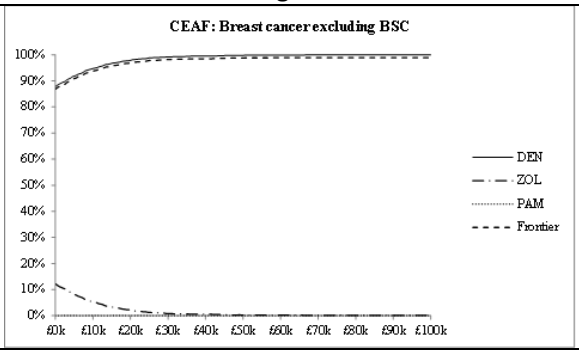
CEAF excluding BSC: all patients



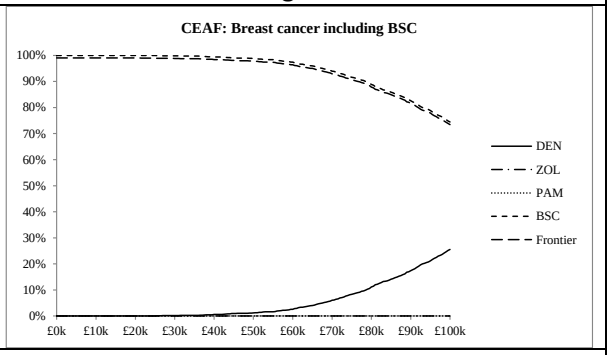
CEAF including BSC: all patients



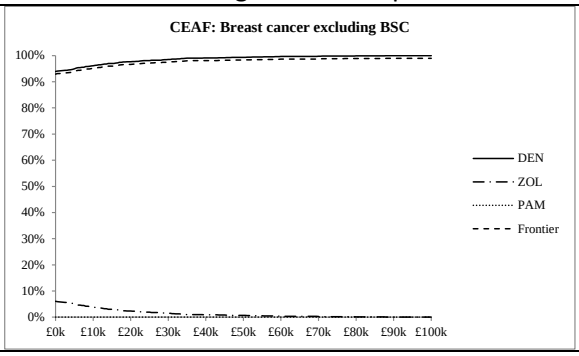
CEAF excluding BSC: SRE naive



CEAF including BSC: SRE naive



CEAF excluding BSC: SRE experienced



CEAF including BSC: SRE experienced

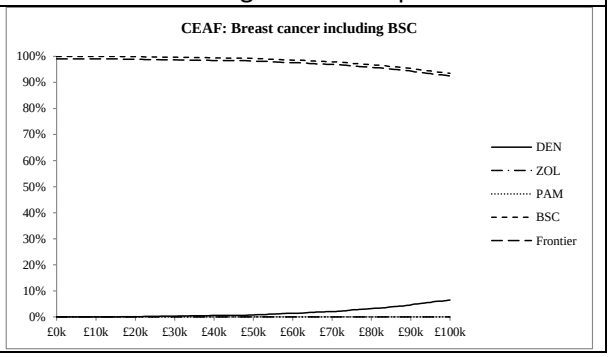


Table 107 Breast cancer univariate sensitivity analyses: All patients

	All patients vs BSC						All patients vs zoledronic acid					
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£6,242	£4,292	-0.988	0.027	£229,547	£157,829	£1,707	-£243	-0.211	0.007	£245,264	Dominant
Amgen STARs	£6,623	£4,673	-0.988	0.027	£243,559	£171,841	£1,782	-£168	-0.211	0.007	£255,996	Dominant
Amgen NMA	£6,324	£4,374	-0.922	0.025	£257,431	£178,053	£1,705	-£245	-0.213	0.007	£242,776	Dominant
Amgen STARs+NMA	£6,683	£4,733	-0.922	0.025	£272,032	£192,655	£1,781	-£170	-0.213	0.007	£253,470	Dominant
No Naive util step	£6,242	£4,292	-0.988	0.017	£366,760	£252,172	£1,707	-£243	-0.211	0.005	£362,999	Dominant
SCC ongoing mean	£6,242	£4,292	-0.988	0.033	£189,204	£130,090	£1,707	-£243	-0.211	0.008	£208,302	Dominant
SCC ongoing max	£6,242	£4,292	-0.988	0.035	£179,091	£123,137	£1,707	-£243	-0.211	0.009	£198,682	Dominant
No gen. mortality	£6,277	£4,316	-0.996	0.027	£228,819	£157,307	£1,717	-£245	-0.213	0.007	£244,512	Dominant
5 yeat horizon	£6,102	£4,204	-0.935	0.025	£239,758	£165,176	£1,670	-£229	-0.199	0.007	£256,441	Dominant
2 year horizon	£4,781	£3,319	-0.653	0.016	£291,409	£202,319	£1,309	-£153	-0.139	0.004	£308,247	Dominant
vd Hout utility	£6,242	£4,292	-0.988	0.025	£249,169	£171,320	£1,707	-£243	-0.211	0.006	£266,094	Dominant
SAE P1+	£6,242	£4,292	-0.988	0.026	£242,970	£167,058	£1,707	-£243	-0.211	0.013	£134,378	Dominant
No SAE	£6,276	£4,300	-1.001	0.028	£224,711	£153,953	£1,773	-£203	-0.214	0.006	£291,955	Dominant
No gen. discs.	£11,493	£7,912	-1.841	0.046	£251,628	£173,216	£3,167	-£414	-0.400	0.012	£259,902	Dominant
No discs.	£11,744	£8,085	-1.883	0.047	£252,493	£173,819	£3,237	-£422	-0.409	0.012	£260,510	Dominant
TTF form AG naive	£6,235	£4,285	-0.994	0.028	£225,904	£155,252	£1,707	-£243	-0.211	0.007	£244,209	Dominant
TTF form AG all	£6,147	£4,197	-1.060	0.030	£205,611	£140,382	£1,687	-£263	-0.227	0.008	£222,101	Dominant

Table 108 Breast cancer SRE patient subgroup effects cost effectiveness results

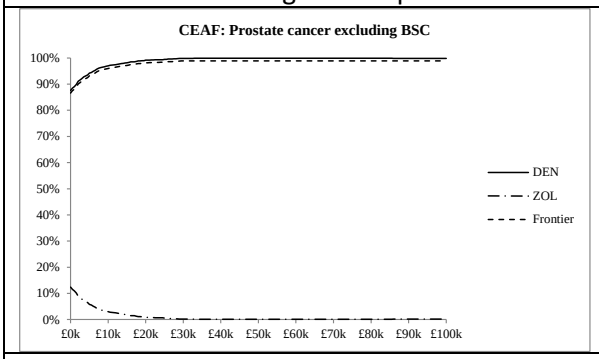
All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	3.159	-0.997	1.821	0.027	[redacted]			£6,227	£232,756
inc PAS								£4,277	£159,866
Zol. Acid	2.383	-0.221	1.841	0.007				£1,693	£259,484
inc PAS								-£258	Dominant
Denosumab	2.162		1.848						
inc PAS									
Pamidronate	2.445	-0.283	1.839	0.009				-£1,317	Dominant
inc PAS								-£3,268	Dominant
SRE Naive	SREs	net	QALYs	net				net	ICER
BSC	2.807	-0.948	1.850	0.034				£6,323	£188,162
inc PAS								£4,373	£130,133
Zol. Acid	2.031	-0.173	1.876	0.007				£1,763	£247,591
inc PAS								-£187	Dominant
Denosumab	1.859		1.883						
inc PAS									
Pamidronate	2.022	-0.163	1.875	0.008				-£1,152	Dominant
inc PAS								-£3,102	Dominant
SRE Exper	SREs	net	QALYs	net				net	ICER
BSC	3.667	-1.069	1.780	0.017				£6,089	£360,413
inc PAS								£4,139	£244,979
Zol. Acid	2.888	-0.290	1.791	0.006				£1,592	£280,994
inc PAS								-£359	Dominant
Denosumab	2.598		1.797						
inc PAS									
Pamidronate	3.055	-0.457	1.786	0.011				-£1,555	Dominant
inc PAS								-£3,505	Dominant

Table 109 Prostate cancer AG NMA cost effectiveness results

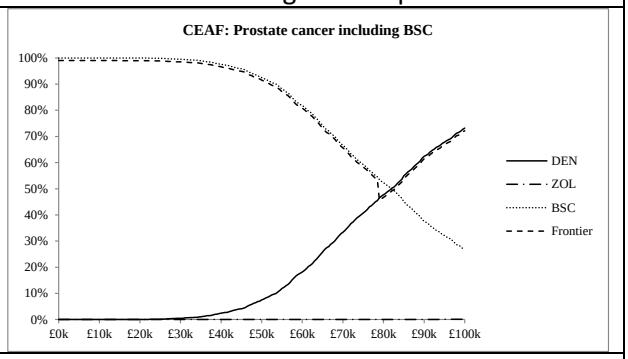
All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	2.185	-0.543	1.065	0.035	[redacted]			£3,951	£112,415
inc PAS								£2,766	£78,713
Zol. Acid	1.772	-0.130	1.090	0.009	[redacted]			£1,059	£111,603
inc PAS								-£125	Dominant
Denosumab	1.642		1.100		[redacted]				
inc PAS									
SRE Naive	SREs	net	QALYs	net	[redacted]			net	ICER
BSC	2.049	-0.528	1.088	0.039	[redacted]			£3,969	£103,003
inc PAS								£2,785	£72,269
Zol. Acid	1.650	-0.129	1.116	0.011	[redacted]			£1,061	£99,561
inc PAS								-£123	Dominant
Denosumab	1.521		1.127		[redacted]				
inc PAS									
SRE Exper	SREs	net	QALYs	net	[redacted]			net	ICER
BSC	2.574	-0.587	0.997	0.025	[redacted]			£3,897	£152,916
inc PAS								£2,713	£106,446
Zol. Acid	2.122	-0.135	1.016	0.006	[redacted]			£1,053	£170,854
inc PAS								-£131	Dominant
Denosumab	1.987		1.023		[redacted]				
inc PAS									

Figure 14 Prostate cancer CEAFs including the PAS

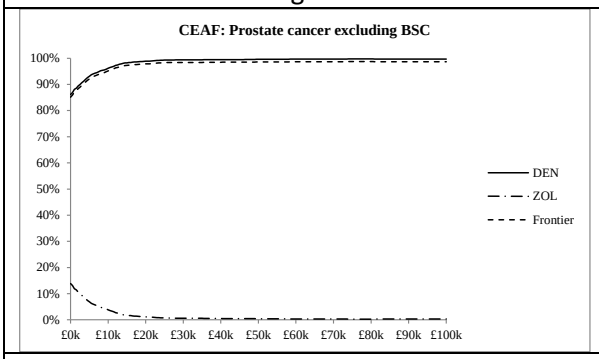
CEAF excluding BSC: all patients



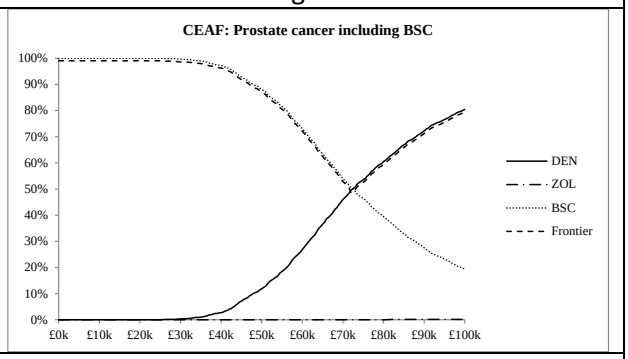
CEAF including BSC: all patients



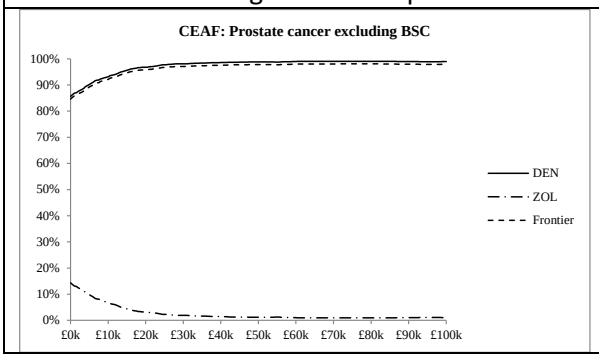
CEAF excluding BSC: SRE naive



CEAF including BSC: SRE naive



CEAF excluding BSC: SRE experienced



CEAF including BSC: SRE experienced

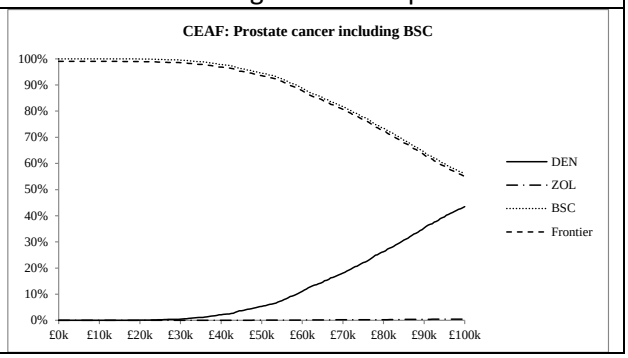


Table 110 Prostate cancer univariate sensitivity analyses: All patients and SRE experienced patients

	SRE naïve patients vs BSC						SRE experienced patients vs zoledronic acid					
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£3,969	£2,785	-0.528	0.039	£103,003	£72,269	£1,053	-£131	-0.135	0.006	£170,854	Dominant
Amgen STARs	£4,195	£3,010	-0.528	0.039	£108,848	£78,114	£1,100	-£84	-0.135	0.006	£178,502	Dominant
Amgen NMA	£3,965	£2,780	-0.532	0.039	£101,900	£71,460	£1,054	-£130	-0.134	0.006	£172,124	Dominant
Amgen STARs+NMA	£4,191	£3,007	-0.532	0.039	£107,716	£77,276	£1,101	-£83	-0.134	0.006	£179,785	Dominant
No Naive util step	£3,969	£2,785	-0.528	0.026	£153,733	£107,862	..	..	..	..	..	..
SCC ongoing mean	£3,969	£2,785	-0.528	0.049	£80,415	£56,420	£1,053	-£131	-0.135	0.009	£116,820	Dominant
SCC ongoing max	£3,969	£2,785	-0.528	0.057	£69,884	£49,032	£1,053	-£131	-0.135	0.011	£95,965	Dominant
No gen. mortality	£4,054	£2,843	-0.546	0.040	£101,176	£70,945	£1,076	-£135	-0.138	0.006	£170,261	Dominant
5 yeat horizon	£3,961	£2,781	-0.520	0.038	£104,689	£73,497	£1,050	-£130	-0.135	0.006	£170,852	Dominant
2 year horizon	£3,620	£2,553	-0.429	0.030	£120,521	£85,018	£959	-£108	-0.122	0.006	£171,394	Dominant
vd Hout utility	£3,969	£2,785	-0.528	0.034	£118,235	£82,955	£1,053	-£131	-0.135	0.005	£195,155	Dominant
SAE P1+	£3,969	£2,785	-0.528	0.024	£162,306	£113,877	£1,053	-£131	-0.135	0.007	£158,518	Dominant
No SAE	£3,983	£2,773	-0.540	0.042	£95,819	£66,716	£1,074	-£135	-0.143	0.007	£159,100	Dominant
No gen. discs.	£7,571	£5,312	-1.037	0.068	£111,073	£77,935	£1,987	-£272	-0.267	0.012	£163,163	Dominant
No discs.	£7,875	£5,526	-1.081	0.071	£111,674	£78,358	£2,169	-£180	-0.298	0.013	£161,126	Dominant
TTF form AG naive	£3,993	£2,809	-0.507	0.037	£107,860	£75,867	..	..	..	..	..	..
TTF form AG all	£3,953	£2,769	-0.541	0.040	£100,060	£70,085	..	..	..	..	..	..

Table 111 Prostate cancer SRE patient subgroup effects cost effectiveness results

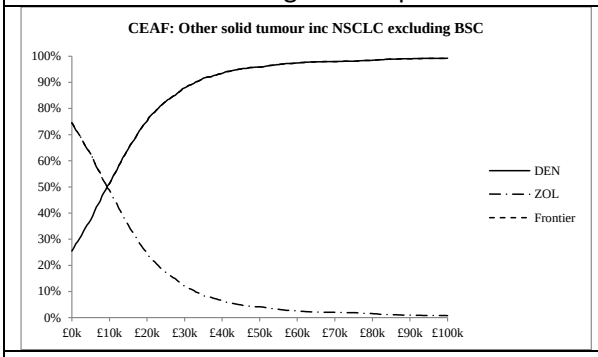
All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	2.185	-0.529	1.065	0.035	[redacted]		[redacted]	£3,968	£113,851
inc PAS								£2,783	£79,865
Zol. Acid	1.772	-0.116	1.090	0.009	[redacted]		[redacted]	£1,076	£117,021
inc PAS								-£109	Dominant
Denosumab	1.656		1.100		[redacted]		[redacted]		
inc PAS									
SRE Naive	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	2.049	-0.526	1.088	0.039	[redacted]		[redacted]	£3,972	£102,016
inc PAS								£2,788	£71,597
Zol. Acid	1.650	-0.126	1.116	0.011	[redacted]		[redacted]	£1,064	£96,209
inc PAS								-£121	Dominant
Denosumab	1.523		1.127		[redacted]		[redacted]		
inc PAS									
SRE Exper	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	2.574	-0.539	0.997	0.023	[redacted]		[redacted]	£3,955	£170,340
inc PAS								£2,770	£119,327
Zol. Acid	2.122	-0.087	1.016	0.004	[redacted]		[redacted]	£1,111	£285,209
inc PAS								-£74	Dominant
Denosumab	2.035		1.020		[redacted]		[redacted]		
inc PAS									

Table 112 OST including lung AG NMA cost effectiveness results

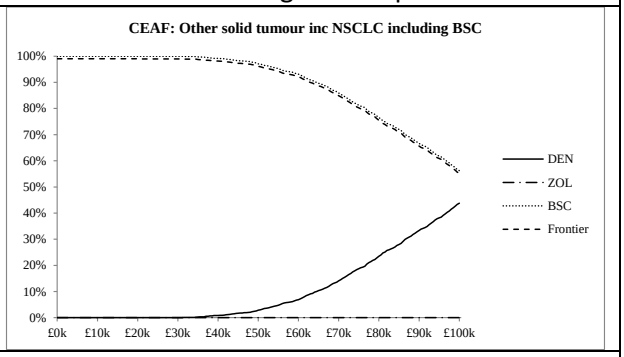
All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	1.606	-0.288	0.703	0.017	[redacted]		[redacted]	£2,548	£147,122
inc PAS								£1,766	£101,986
Zol. Acid	1.410	-0.092	0.714	0.006	[redacted]		[redacted]	£836	£139,739
inc PAS								£54	£9,004
Denosumab	1.318		0.720		[redacted]		[redacted]		
inc PAS									
SRE Naive	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	1.598	-0.343	0.716	0.024	[redacted]		[redacted]	£2,473	£103,350
inc PAS								£1,691	£70,679
Zol. Acid	1.358	-0.103	0.732	0.008	[redacted]		[redacted]	£823	£106,812
inc PAS								£41	£5,337
Denosumab	1.255		0.740		[redacted]		[redacted]		
inc PAS									
SRE Exper	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	1.614	-0.235	0.691	0.011	[redacted]		[redacted]	£2,620	£238,840
inc PAS								£1,839	£167,587
Zol. Acid	1.460	-0.082	0.697	0.004	[redacted]		[redacted]	£848	£196,114
inc PAS								£66	£15,282
Denosumab	1.378		0.702		[redacted]		[redacted]		
inc PAS									

Figure 15 OST+Lung cancer CEAFs including the PAS

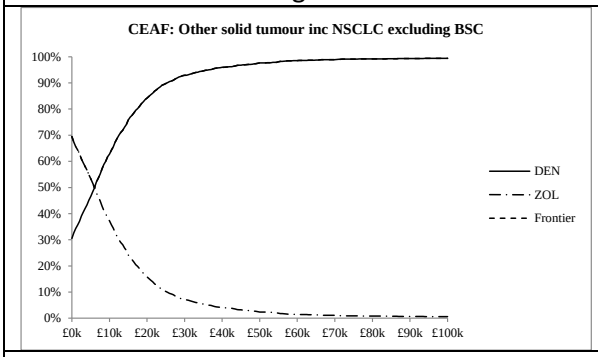
CEAF excluding BSC: all patients



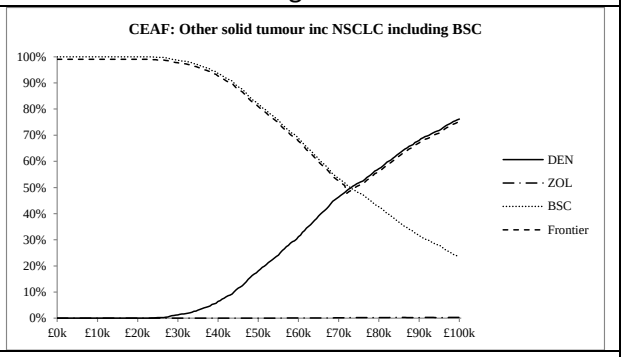
CEAF including BSC: all patients



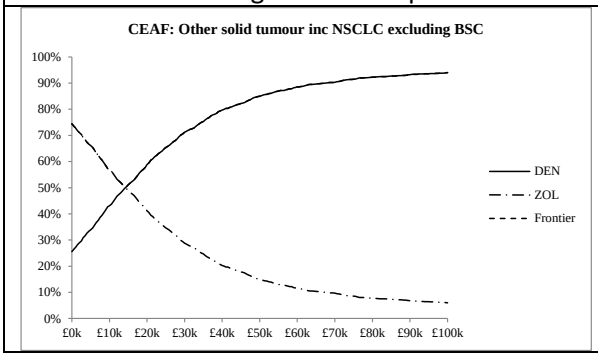
CEAF excluding BSC: SRE naive



CEAF including BSC: SRE naive



CEAF excluding BSC: SRE experienced



CEAF including BSC: SRE experienced

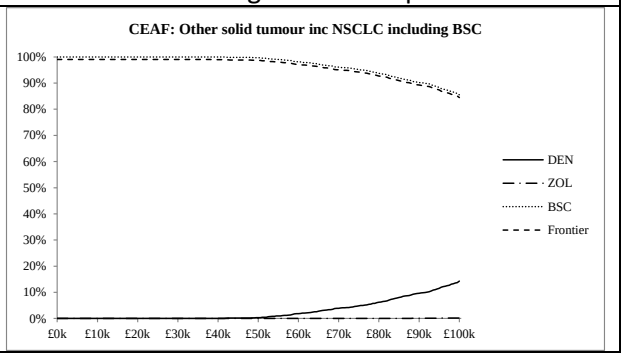


Table 113 OST + lung cancer univariate sensitivity analyses: All patients and SRE experienced patients

	SRE naïve patients vs BSC						SRE experienced patients vs zoledronic acid					
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,473	£1,691	-0.343	0.024	£103,350	£70,679	£848	£66	-0.082	0.004	£196,114	£15,282
Amgen STARs	£2,618	£1,836	-0.343	0.024	£109,409	£76,737	£869	£87	-0.082	0.004	£200,948	£20,115
Amgen NMA	£2,509	£1,727	-0.320	0.022	£112,789	£77,644	£849	£68	-0.081	0.004	£198,534	£15,801
Amgen STARs+NMA	£2,646	£1,864	-0.320	0.022	£118,943	£83,798	£870	£88	-0.081	0.004	£203,338	£20,606
No Naive util step	£2,473	£1,691	-0.343	0.018	£135,660	£92,775	..	..	..	..	..	..
SCC ongoing mean	£2,473	£1,691	-0.343	0.027	£90,853	£62,132	£848	£66	-0.082	0.005	£164,375	£12,808
SCC ongoing max	£2,473	£1,691	-0.343	0.030	£82,514	£56,429	£848	£66	-0.082	0.006	£144,789	£11,282
No gen. mortality	£2,481	£1,696	-0.344	0.024	£103,033	£70,452	£851	£67	-0.082	0.004	£195,987	£15,403
5 year horizon	£2,476	£1,695	-0.338	0.024	£105,289	£72,086	£845	£65	-0.082	0.004	£196,090	£15,025
2 year horizon	£2,385	£1,639	-0.311	0.021	£113,714	£78,167	£788	£42	-0.076	0.004	£195,766	£10,537
vd Hout utility	£2,473	£1,691	-0.343	0.020	£124,310	£85,013	£848	£66	-0.082	0.004	£237,589	£18,514
SAE P1+	£2,473	£1,691	-0.343	0.020	£122,918	£84,061	£848	£66	-0.082	0.008	£107,304	£8,361
No SAE	£2,459	£1,671	-0.345	0.025	£98,978	£67,269	£846	£58	-0.083	0.004	£204,488	£14,044
No gen. discs.	£5,895	£4,064	-0.760	0.049	£120,402	£83,010	£1,630	-£201	-0.172	0.009	£176,418	Dominant
No discs.	£6,040	£4,165	-0.777	0.050	£121,082	£83,502	£1,696	-£178	-0.179	0.010	£176,813	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	£2,475	£1,693	-0.339	0.024	£103,297	£70,666	..	..	..	..	..	..

Table 114 OST including lung SRE patient subgroup effects cost effectiveness results

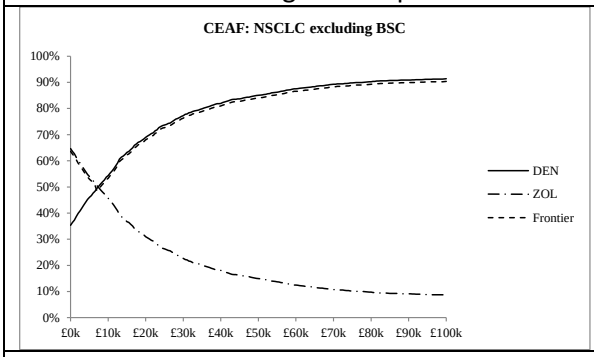
All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	1.606	-0.255	0.703	0.016	[redacted]		[redacted]	£2,606	£164,322
inc PAS								£1,824	£115,025
Zol. Acid	1.410	-0.059	0.714	0.005	[redacted]		[redacted]	£893	£197,725
inc PAS								£112	£24,686
Denosumab	1.352		0.719		[redacted]		[redacted]		
inc PAS									
SRE Naive	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	1.598	-0.341	0.716	0.024	[redacted]		[redacted]	£2,477	£102,060
inc PAS								£1,695	£69,845
Zol. Acid	1.358	-0.102	0.732	0.008	[redacted]		[redacted]	£827	£102,773
inc PAS								£45	£5,580
Denosumab	1.257		0.740		[redacted]		[redacted]		
inc PAS									
SRE Exper	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	1.614	-0.171	0.691	0.008	[redacted]		[redacted]	£2,730	£350,937
inc PAS								£1,948	£250,441
Zol. Acid	1.460	-0.018	0.697	0.001	[redacted]		[redacted]	£957	£846,749
inc PAS								£176	£155,285
Denosumab	1.443		0.698		[redacted]		[redacted]		
inc PAS									

Table 115 Lung cancer AG NMA cost effectiveness results

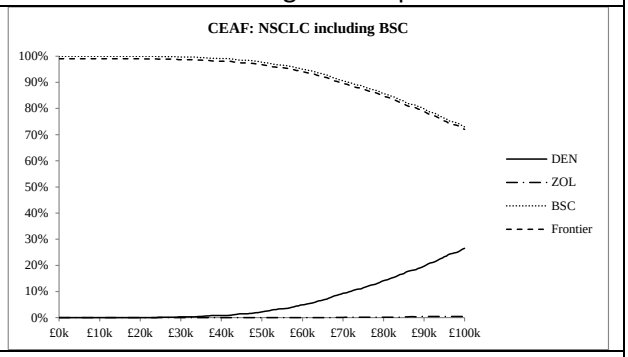
All Patients	SREs	net	QALYs	net	Tx Costs	net	All Costs	net	ICER
BSC	0.952	-0.218	0.441	0.012	[redacted]		[redacted]	£2,262	£191,412
inc PAS								£1,583	£133,926
Zol. Acid	0.809	-0.076	0.448	0.005	[redacted]		[redacted]	£708	£149,878
inc PAS								£28	£5,972
Denosumab	0.734		0.453		[redacted]		[redacted]		
inc PAS									
SRE Naive	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	0.886	-0.228	0.455	0.014	[redacted]		[redacted]	£2,257	£158,333
inc PAS								£1,578	£110,671
Zol. Acid	0.746	-0.087	0.463	0.006	[redacted]		[redacted]	£693	£112,617
inc PAS								£13	£2,135
Denosumab	0.659		0.470		[redacted]		[redacted]		
inc PAS									
SRE Exper	SREs	net	QALYs	net	[redacted]		[redacted]	net	ICER
BSC	1.015	-0.210	0.427	0.009	[redacted]		[redacted]	£2,268	£239,211
inc PAS								£1,588	£167,529
Zol. Acid	0.870	-0.065	0.433	0.003	[redacted]		[redacted]	£722	£215,614
inc PAS								£43	£12,743
Denosumab	0.806		0.437		[redacted]		[redacted]		
inc PAS									

Figure 16 Lung cancer CEAFs including the PAS

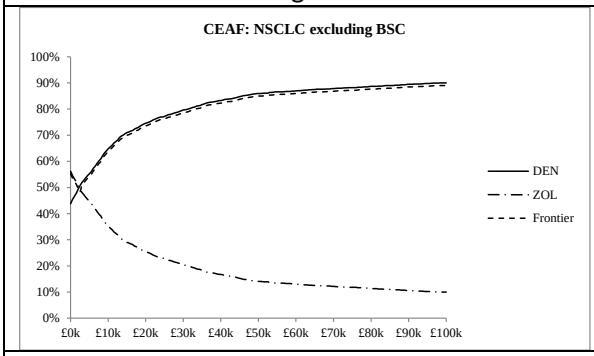
CEAF excluding BSC: all patients



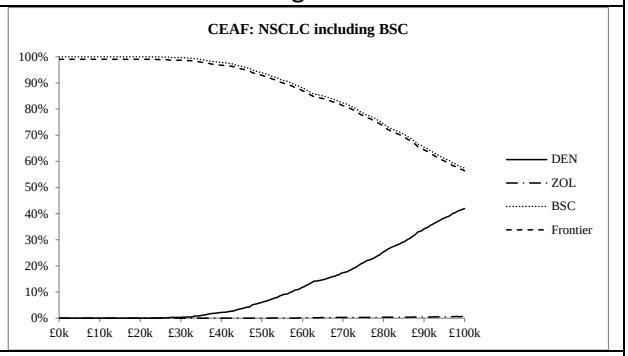
CEAF including BSC: all patients



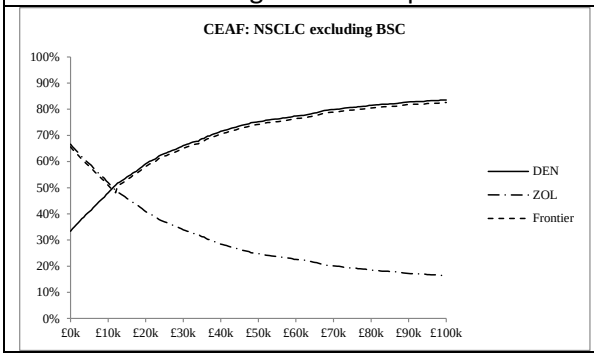
CEAF excluding BSC: SRE naive



CEAF including BSC: SRE naive



CEAF excluding BSC: SRE experienced



CEAF including BSC: SRE experienced

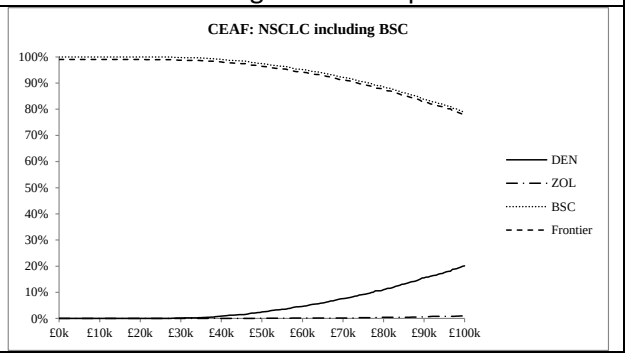


Table 116 Lung cancer univariate sensitivity analyses: All patients and SRE experienced patients

	SRE naïve patients vs BSC						SRE experienced patients vs zoledronic acid					
	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,257	£1,578	-0.228	0.014	£158,333	£110,671	£722	£43	-0.065	0.003	£215,614	£12,743
Amgen STARs	£2,359	£1,679	-0.228	0.014	£165,463	£117,801	£738	£58	-0.065	0.003	£220,231	£17,361
Amgen NMA	£2,257	£1,578	-0.228	0.014	£158,333	£110,671	£722	£43	-0.065	0.003	£215,614	£12,743
Amgen STARs+NMA	£2,359	£1,679	-0.228	0.014	£165,463	£117,801	£738	£58	-0.065	0.003	£220,231	£17,361
No Naive util step	£2,257	£1,578	-0.228	0.011	£199,936	£139,750	..	..	..	..	..	..
SCC ongoing mean	£2,257	£1,578	-0.228	0.015	£149,443	£104,457	£722	£43	-0.065	0.004	£200,348	£11,841
SCC ongoing max	£2,257	£1,578	-0.228	0.016	£142,745	£99,775	£722	£43	-0.065	0.004	£189,156	£11,180
No gen. mortality	£2,263	£1,582	-0.228	0.014	£158,064	£110,477	£725	£43	-0.065	0.003	£215,469	£12,821
5 year horizon	£2,257	£1,578	-0.227	0.014	£158,499	£110,792	£722	£43	-0.065	0.003	£215,613	£12,735
2 year horizon	£2,227	£1,559	-0.218	0.013	£165,275	£115,737	£703	£36	-0.063	0.003	£215,451	£10,888
vd Hout utility	£2,257	£1,578	-0.228	0.011	£205,154	£143,397	£722	£43	-0.065	0.003	£279,244	£16,504
SAE P1+	£2,257	£1,578	-0.228	0.013	£177,449	£124,032	£722	£43	-0.065	0.005	£147,641	£8,726
No SAE	£2,243	£1,559	-0.229	0.015	£149,896	£104,205	£719	£35	-0.065	0.003	£227,229	£11,032
No gen. discs.	£3,885	£2,737	-0.343	0.020	£191,622	£135,008	£1,046	-£102	-0.096	0.005	£204,827	Dominant
No discs.	£3,926	£2,766	-0.346	0.020	£192,291	£135,497	£1,064	-£96	-0.097	0.005	£204,801	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	..	..	..	..	..	..	..	..	..	..	..	..

Table 117 Summary of results denosumab versus zoledronic acid

		Breast cancer		Prostate cancer		OST+Lung		Lung cancer	
		ex PAS	inc PAS	ex PAS	inc PAS	ex PAS	inc PAS	ex PAS	inc PAS
Manufacturer: pooled RR&HR									
All	Δ Cost	£1,484	-£483						
	Δ QALY	0.007							
	ICER	£203,387	dominant						
Exper.	Δ Cost			£922	-£281	£757	-£43		
	Δ QALY			0.006		0.004			
	ICER			£157,276	dominant	£205,580	dominant		
AG modelling: pooled RR&HR									
All	Δ Cost	£1,707	-£243	£1,059	-£125	£836	£54	£708	£28
	Δ QALY	0.007	0.007	0.009	0.009	0.006	0.006	0.005	0.005
	ICER	£245,264	Dominant	£111,603	Dominant	£139,739	£9,004	£149,878	£5,972
Naive	Δ Cost	£1,747	-£203	£1,061	-£123	£823	£41	£693	£13
	Δ QALY	0.008	0.008	0.011	0.011	0.008	0.008	0.006	0.006
	ICER	£209,345	Dominant	£99,561	Dominant	£106,812	£5,337	£112,617	£2,135
Exper.	Δ Cost	£1,649	-£301	£1,053	-£131	£848	£66	£722	£43
	Δ QALY	0.005	0.005	0.006	0.006	0.004	0.004	0.003	0.003
	ICER	£332,185	Dominant	£170,854	Dominant	£196,114	£15,282	£215,614	£12,743
AG modelling: SRE naïve and SRE experienced specific HRs+RRs									
All	Δ Cost	£1,693	-£258	£1,076	-£109	£893	£112	£708	£28
	Δ QALY	0.007	0.007	0.009	0.009	0.005	0.005	0.005	0.005
	ICER	£259,484	Dominant	£117,021	Dominant	£197,725	£24,686	£149,878	£5,972
Naive	Δ Cost	£1,763	-£187	£1,064	-£121	£827	£45	£693	£13
	Δ QALY	0.007	0.007	0.011	0.011	0.008	0.008	0.006	0.006
	ICER	£247,591	Dominant	£96,209	Dominant	£102,773	£5,580	£112,617	£2,135
Exper.	Δ Cost	£1,592	-£359	£1,111	-£74	£957	£176	£722	£43
	Δ QALY	0.006	0.006	0.004	0.004	0.001	0.001	0.003	0.003
	ICER	£280,994	Dominant	£285,209	Dominant	£846,749	£155,285	£215,614	£12,743

Table 118 Summary of results denosumab versus BSC

		Breast cancer		Prostate cancer		OST+Lung		Lung cancer	
		ex PAS	inc PAS	ex PAS	inc PAS	ex PAS	inc PAS	ex PAS	inc PAS
Manufacturer: pooled RR&HR									
Naive	Δ Cost			£3,993	£2,790	£2,530	£1,730		
	Δ QALY			0.039		0.021			
	ICER			£102,067	£71,320	£122,499	£83,763		
AG modelling: pooled RR&HR									
All	Δ Cost	£6,242	£4,292	£3,951	£2,766	£2,548	£1,766	£2,262	£1,583
	Δ QALY	0.027	0.027	0.035	0.035	0.017	0.017	0.012	0.012
	ICER	£229,547	£157,829	£112,415	£78,713	£147,122	£101,986	£191,412	£133,926
Naive	Δ Cost	£6,308	£4,358	£3,969	£2,785	£2,473	£1,691	£2,257	£1,578
	Δ QALY	0.035	0.035	0.039	0.039	0.024	0.024	0.014	0.014
	ICER	£181,092	£125,109	£103,003	£72,269	£103,350	£70,679	£158,333	£110,671
Exper.	Δ Cost	£6,146	£4,196	£3,897	£2,713	£2,620	£1,839	£2,268	£1,588
	Δ QALY	0.016	0.016	0.025	0.025	0.011	0.011	0.009	0.009
	ICER	£379,539	£259,113	£152,916	£106,446	£238,840	£167,587	£239,211	£167,529
AG modelling: SRE naïve and SRE experienced specific HRs+RRs									
All	Δ Cost	£6,227	£4,277	£3,968	£2,783	£2,606	£1,824	£2,262	£1,583
	Δ QALY	0.027	0.027	0.035	0.035	0.016	0.016	0.012	0.012
	ICER	£232,756	£159,866	£113,851	£79,865	£164,322	£115,025	£191,412	£133,926
Naive	Δ Cost	£6,323	£4,373	£3,972	£2,788	£2,477	£1,695	£2,257	£1,578
	Δ QALY	0.034	0.034	0.039	0.039	0.024	0.024	0.014	0.014
	ICER	£188,162	£130,133	£102,016	£71,597	£102,060	£69,845	£158,333	£110,671
Exper.	Δ Cost	£6,089	£4,139	£3,955	£2,770	£2,730	£1,948	£2,268	£1,588
	Δ QALY	0.017	0.017	0.023	0.023	0.008	0.008	0.009	0.009
	ICER	£360,413	£244,979	£170,340	£119,327	£350,937	£250,441	£239,211	£167,529

APPENDIX 15 UNIVARIATE AND PROBABILISTIC SENSITIVITY ANALYSES

A range of univariate sensitivity analyses have been explored:

	Description	**Abbreviated**
SA01	Base Case	Base Case
SA02	Amgen STARs costing	Amgen STARs
SA03	Amgen NMA results	Amgen NMA
SA04	Amgen STARs costings and NMA results	Amgen STARs+NMA
SA05	No HRQoL step change for naive to experienced	No Naive util step
SA06	SCC permanent utility effect of the average P1-P5 decrement	SCC ongoing mean
SA07	SCC permanent utility effect of the maximum P1-P5 decrement	SCC ongoing max
SA08	No general mortality	No gen. mortality
SA09	5 year horizon	5 year horizon
SA10	2 year horizon	2 year horizon
SA11	vdHOUT utility multipliers	vd Hout utility
SA12	QoL impact SAEs ONJ and renal cohort average survival, not the measured trial duration	SAE P1+
SA13	Excluding SAEs	No SAE
SA14	No general discontinuations	No gen. discs.
SA15	No discontinuations	No discs.
SA16	AG TTF functional form from NAIVE for breast and prostate	TTF form AG naive
SA17	AG TTF functional form all patients for breast, prostate and OSTL	TTF form AG all patients

These are presented for the four cancer groupings: breast (BRST), prostate (PROS), other solid tumour including lung (OSTL) and lung (LUNG). They are also presented for the three patient groups of all, naïve and experiences, coupled with the split between applying the pooled HRs and RRs and the SRE specific HRs and RRs for breast (BRST), prostate (PROS), other solid tumour including lung (OSTL). The summaries that follow all show the net impact of denosumab on total amounts. The costs reported are the total costs including SRE costs and SAE costs: e.g. the cost associated with BSC ex PAS is the additional cost of using denosumab compared to BSC. These sensitivity analyses are only presented for the analyses that apply the pooled HRs and RRs. The parallel sensitivity analyses that present them for the analyses that apply the SRE experience subgroup specific HRs and RRs are available on demand from the AG.
The probabilistic analyses were run over 2,000 iterations. As a cross check the ALL PATIENTs probabilistic modelling was re-run with 10,000 iterations with results being near identical to those of the run with 2,000 iterations.

Univariate sensitivity analyses: Breast Cancer

BREAST ALL PATIENTS	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£6,242	£4,292	-0.988	0.027	£229,547	£157,829	£1,707	-£243	-0.211	0.007	£245,264	Dominant
Amgen STARs	£6,623	£4,673	-0.988	0.027	£243,559	£171,841	£1,782	-£168	-0.211	0.007	£255,996	Dominant
Amgen NMA	£6,324	£4,374	-0.922	0.025	£257,431	£178,053	£1,705	-£245	-0.213	0.007	£242,776	Dominant
Amgen STARs+NMA	£6,683	£4,733	-0.922	0.025	£272,032	£192,655	£1,781	-£170	-0.213	0.007	£253,470	Dominant
No Naive util step	£6,242	£4,292	-0.988	0.017	£366,760	£252,172	£1,707	-£243	-0.211	0.005	£362,999	Dominant
SCC ongoing mean	£6,242	£4,292	-0.988	0.033	£189,204	£130,090	£1,707	-£243	-0.211	0.008	£208,302	Dominant
SCC ongoing max	£6,242	£4,292	-0.988	0.035	£179,091	£123,137	£1,707	-£243	-0.211	0.009	£198,682	Dominant
No gen. mortality	£6,277	£4,316	-0.996	0.027	£228,819	£157,307	£1,717	-£245	-0.213	0.007	£244,512	Dominant
5 year horizon	£6,102	£4,204	-0.935	0.025	£239,758	£165,176	£1,670	-£229	-0.199	0.007	£256,441	Dominant
2 year horizon	£4,781	£3,319	-0.653	0.016	£291,409	£202,319	£1,309	-£153	-0.139	0.004	£308,247	Dominant
vd Hout utility	£6,242	£4,292	-0.988	0.025	£249,169	£171,320	£1,707	-£243	-0.211	0.006	£266,094	Dominant
SAE P1+	£6,242	£4,292	-0.988	0.026	£242,970	£167,058	£1,707	-£243	-0.211	0.013	£134,378	Dominant
No SAE	£6,276	£4,300	-1.001	0.028	£224,711	£153,953	£1,773	-£203	-0.214	0.006	£291,955	Dominant
No gen. discs.	£11,493	£7,912	-1.841	0.046	£251,628	£173,216	£3,167	-£414	-0.400	0.012	£259,902	Dominant
No discs.	£11,744	£8,085	-1.883	0.047	£252,493	£173,819	£3,237	-£422	-0.409	0.012	£260,510	Dominant
TTF form AG naive	£6,235	£4,285	-0.994	0.028	£225,904	£155,252	£1,707	-£243	-0.211	0.007	£244,209	Dominant
TTF form AG all	£6,147	£4,197	-1.060	0.030	£205,611	£140,382	£1,687	-£263	-0.227	0.008	£222,101	Dominant

BREAST SRE NAIVE	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£6,308	£4,358	-0.962	0.035	£181,092	£125,109	£1,747	-£203	-0.186	0.008	£209,345	Dominant
Amgen STARs	£6,674	£4,724	-0.962	0.035	£191,585	£135,602	£1,812	-£138	-0.186	0.008	£217,069	Dominant
Amgen NMA	£6,432	£4,482	-0.863	0.031	£210,330	£146,564	£1,745	-£205	-0.189	0.008	£206,251	Dominant
Amgen STARs+NMA	£6,764	£4,814	-0.863	0.031	£221,185	£157,419	£1,810	-£140	-0.189	0.008	£213,963	Dominant
No Naive util step	£6,308	£4,358	-0.962	0.018	£358,586	£247,732	£1,747	-£203	-0.186	0.005	£386,508	Dominant
SCC ongoing mean	£6,308	£4,358	-0.962	0.040	£157,346	£108,704	£1,747	-£203	-0.186	0.009	£187,157	Dominant
SCC ongoing max	£6,308	£4,358	-0.962	0.042	£150,985	£104,309	£1,747	-£203	-0.186	0.010	£180,993	Dominant
No gen. mortality	£6,343	£4,381	-0.970	0.035	£180,337	£124,558	£1,757	-£205	-0.188	0.008	£208,454	Dominant
5 year horizon	£6,185	£4,287	-0.895	0.032	£192,083	£133,134	£1,714	-£185	-0.172	0.008	£223,148	Dominant
2 year horizon	£4,902	£3,441	-0.585	0.020	£250,927	£176,109	£1,355	-£106	-0.109	0.005	£292,125	Dominant
vd Hout utility	£6,308	£4,358	-0.962	0.032	£196,932	£136,052	£1,747	-£203	-0.186	0.008	£227,647	Dominant
SAE P1+	£6,308	£4,358	-0.962	0.033	£189,253	£130,747	£1,747	-£203	-0.186	0.014	£124,016	Dominant
No SAE	£6,344	£4,367	-0.974	0.036	£178,058	£122,590	£1,814	-£162	-0.189	0.007	£242,829	Dominant
No gen. discs.	£11,657	£8,075	-1.750	0.056	£208,350	£144,337	£3,251	-£331	-0.344	0.014	£231,276	Dominant
No discs.	£11,913	£8,253	-1.788	0.057	£209,438	£145,104	£3,323	-£336	-0.351	0.014	£232,177	Dominant
TTF form AG naive	£6,297	£4,347	-0.971	0.036	£177,244	£122,356	£1,748	-£202	-0.186	0.008	£208,080	Dominant
TTF form AG all	£6,148	£4,198	-1.083	0.039	£155,959	£106,487	£1,713	-£237	-0.213	0.009	£181,811	Dominant

BREAST SRE EXPER	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£6,146	£4,196	-1.025	0.016	£379,539	£259,113	£1,649	-£301	-0.247	0.005	£332,185	Dominant
Amgen STARs	£6,549	£4,599	-1.025	0.016	£404,445	£284,020	£1,738	-£212	-0.247	0.005	£350,196	Dominant
Amgen NMA	£6,169	£4,219	-1.008	0.016	£387,700	£265,144	£1,649	-£301	-0.247	0.005	£332,393	Dominant
Amgen STARs+NMA	£6,566	£4,616	-1.008	0.016	£412,664	£290,108	£1,738	-£212	-0.247	0.005	£350,402	Dominant
No Naive util step	..	..	..	..	..	..	..	..	..	..	..	..
SCC ongoing mean	£6,146	£4,196	-1.025	0.023	£269,923	£184,278	£1,649	-£301	-0.247	0.007	£251,665	Dominant
SCC ongoing max	£6,146	£4,196	-1.025	0.025	£247,002	£168,630	£1,649	-£301	-0.247	0.007	£233,481	Dominant
No gen. mortality	£6,183	£4,221	-1.032	0.016	£379,385	£259,009	£1,659	-£303	-0.249	0.005	£332,076	Dominant
5 year horizon	£5,982	£4,084	-0.993	0.016	£380,130	£259,517	£1,606	-£292	-0.240	0.005	£332,629	Dominant
2 year horizon	£4,607	£3,145	-0.751	0.012	£387,023	£264,223	£1,241	-£221	-0.182	0.004	£337,521	Dominant
vd Hout utility	£6,146	£4,196	-1.025	0.015	£409,664	£279,680	£1,649	-£301	-0.247	0.005	£358,405	Dominant
SAE P1+	£6,146	£4,196	-1.025	0.015	£418,347	£285,608	£1,649	-£301	-0.247	0.011	£154,000	Dominant
No SAE	£6,178	£4,202	-1.040	0.017	£366,663	£249,381	£1,714	-£262	-0.251	0.004	£421,982	Dominant
No gen. discs.	£11,257	£7,676	-1.973	0.031	£364,430	£248,487	£3,047	-£535	-0.481	0.009	£320,879	Dominant
No discs.	£11,501	£7,842	-2.020	0.032	£364,043	£248,215	£3,114	-£546	-0.492	0.010	£320,590	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	..	..	..	..	..	..	..	..	..	..	..	..

Univariate sensitivity analyses: Prostate Cancer

PROSTATE ALL PATIENTS	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£3,951	£2,766	-0.543	0.035	£112,415	£78,713	£1,059	-£125	-0.130	0.009	£111,603	Dominant
Amgen STARs	£4,179	£2,995	-0.543	0.035	£118,915	£85,213	£1,106	-£79	-0.130	0.009	£116,525	Dominant
Amgen NMA	£3,948	£2,764	-0.546	0.035	£111,558	£78,091	£1,060	-£124	-0.129	0.009	£112,659	Dominant
Amgen STARs+NMA	£4,177	£2,993	-0.546	0.035	£118,030	£84,563	£1,107	-£78	-0.129	0.009	£117,594	Dominant
No Naive util step	£3,951	£2,766	-0.543	0.026	£153,522	£107,497	£1,059	-£125	-0.130	0.007	£159,704	Dominant
SCC ongoing mean	£3,951	£2,766	-0.543	0.046	£85,204	£59,660	£1,059	-£125	-0.130	0.012	£86,925	Dominant
SCC ongoing max	£3,951	£2,766	-0.543	0.054	£73,053	£51,152	£1,059	-£125	-0.130	0.014	£75,460	Dominant
No gen. mortality	£4,037	£2,825	-0.560	0.036	£110,722	£77,494	£1,081	-£131	-0.134	0.010	£109,732	Dominant
5 yeat horizon	£3,941	£2,761	-0.537	0.035	£113,896	£79,787	£1,057	-£123	-0.129	0.009	£113,427	Dominant
2 year horizon	£3,591	£2,524	-0.454	0.028	£127,528	£89,659	£973	-£93	-0.109	0.008	£129,289	Dominant
vd Hout utility	£3,951	£2,766	-0.543	0.031	£128,929	£90,277	£1,059	-£125	-0.130	0.008	£127,983	Dominant
SAE P1+	£3,951	£2,766	-0.543	0.021	£187,561	£131,331	£1,059	-£125	-0.130	0.010	£106,232	Dominant
No SAE	£3,963	£2,754	-0.556	0.038	£103,941	£72,218	£1,081	-£129	-0.138	0.010	£106,466	Dominant
No gen. discs.	£7,529	£5,270	-1.073	0.064	£118,284	£82,795	£2,011	-£248	-0.246	0.017	£119,642	Dominant
No discs.	£7,831	£5,481	-1.119	0.066	£118,739	£83,114	£2,198	-£152	-0.273	0.018	£120,679	Dominant
TTF form AG naive	£3,968	£2,784	-0.528	0.034	£116,636	£81,823	£1,065	-£120	-0.125	0.009	£116,751	Dominant
TTF form AG all	£3,939	£2,755	-0.553	0.036	£109,826	£76,803	£1,056	-£129	-0.133	0.010	£108,797	Dominant

PROSTATE NAIVE	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£3,969	£2,785	-0.528	0.039	£103,003	£72,269	£1,061	-£123	-0.129	0.011	£99,561	Dominant
Amgen STARs	£4,195	£3,010	-0.528	0.039	£108,848	£78,114	£1,107	-£77	-0.129	0.011	£103,929	Dominant
Amgen NMA	£3,965	£2,780	-0.532	0.039	£101,900	£71,460	£1,062	-£122	-0.128	0.011	£100,547	Dominant
Amgen STARs+NMA	£4,191	£3,007	-0.532	0.039	£107,716	£77,276	£1,108	-£76	-0.128	0.011	£104,926	Dominant
No Naive util step	£3,969	£2,785	-0.528	0.026	£153,733	£107,862	£1,061	-£123	-0.129	0.007	£156,150	Dominant
SCC ongoing mean	£3,969	£2,785	-0.528	0.049	£80,415	£56,420	£1,061	-£123	-0.129	0.013	£79,802	Dominant
SCC ongoing max	£3,969	£2,785	-0.528	0.057	£69,884	£49,032	£1,061	-£123	-0.129	0.015	£70,226	Dominant
No gen. mortality	£4,054	£2,843	-0.546	0.040	£101,176	£70,945	£1,082	-£129	-0.133	0.011	£97,612	Dominant
5 yeat horizon	£3,961	£2,781	-0.520	0.038	£104,689	£73,497	£1,060	-£120	-0.126	0.010	£101,544	Dominant
2 year horizon	£3,620	£2,553	-0.429	0.030	£120,521	£85,018	£979	-£88	-0.105	0.008	£119,210	Dominant
vd Hout utility	£3,969	£2,785	-0.528	0.034	£118,235	£82,955	£1,061	-£123	-0.129	0.009	£114,266	Dominant
SAE P1+	£3,969	£2,785	-0.528	0.024	£162,306	£113,877	£1,061	-£123	-0.129	0.011	£95,272	Dominant
No SAE	£3,983	£2,773	-0.540	0.042	£95,819	£66,716	£1,083	-£126	-0.136	0.011	£95,462	Dominant
No gen. discs.	£7,571	£5,312	-1.037	0.068	£111,073	£77,935	£2,020	-£239	-0.239	0.018	£109,544	Dominant
No discs.	£7,875	£5,526	-1.081	0.071	£111,674	£78,358	£2,208	-£142	-0.265	0.020	£111,053	Dominant
TTF form AG naive	£3,993	£2,809	-0.507	0.037	£107,860	£75,867	£1,069	-£116	-0.122	0.010	£105,215	Dominant
TTF form AG all	£3,953	£2,769	-0.541	0.040	£100,060	£70,085	£1,057	-£128	-0.132	0.011	£96,521	Dominant

PROSTATE EXPER	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£3,897	£2,713	-0.587	0.025	£152,916	£106,446	£1,053	-£131	-0.135	0.006	£170,854	Dominant
Amgen STARs	£4,135	£2,950	-0.587	0.025	£162,234	£115,764	£1,100	-£84	-0.135	0.006	£178,502	Dominant
Amgen NMA	£3,900	£2,716	-0.584	0.025	£153,710	£107,034	£1,054	-£130	-0.134	0.006	£172,124	Dominant
Amgen STARs+NMA	£4,137	£2,953	-0.584	0.025	£163,045	£116,368	£1,101	-£83	-0.134	0.006	£179,785	Dominant
No Naive util step	..	..	..	..	..	..	..	..	..	..	..	..
SCC ongoing mean	£3,897	£2,713	-0.587	0.038	£102,981	£71,686	£1,053	-£131	-0.135	0.009	£116,820	Dominant
SCC ongoing max	£3,897	£2,713	-0.587	0.046	£84,108	£58,549	£1,053	-£131	-0.135	0.011	£95,965	Dominant
No gen. mortality	£3,986	£2,775	-0.601	0.026	£152,326	£106,035	£1,076	-£135	-0.138	0.006	£170,261	Dominant
5 yeat horizon	£3,884	£2,703	-0.584	0.025	£152,944	£106,466	£1,050	-£130	-0.135	0.006	£170,852	Dominant
2 year horizon	£3,509	£2,442	-0.524	0.023	£153,779	£107,047	£959	-£108	-0.122	0.006	£171,394	Dominant
vd Hout utility	£3,897	£2,713	-0.587	0.022	£174,747	£121,643	£1,053	-£131	-0.135	0.005	£195,155	Dominant
SAE P1+	£3,897	£2,713	-0.587	0.011	£341,668	£237,838	£1,053	-£131	-0.135	0.007	£158,518	Dominant
No SAE	£3,909	£2,699	-0.600	0.028	£137,816	£95,166	£1,074	-£135	-0.143	0.007	£159,100	Dominant
No gen. discs.	£7,408	£5,149	-1.176	0.051	£145,820	£101,357	£1,987	-£272	-0.267	0.012	£163,163	Dominant
No discs.	£7,704	£5,355	-1.227	0.053	£145,522	£101,143	£2,169	-£180	-0.298	0.013	£161,126	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	..	..	..	..	..	..	..	..	..	..	..	..

Univariate sensitivity analyses: OST+NSCLC

OST+NSCLC	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
ALL PATIENTS	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,548	£1,766	-0.288	0.017	£147,122	£101,986	£836	£54	-0.092	0.006	£139,739	£9,004
Amgen STARs	£2,676	£1,894	-0.288	0.017	£154,479	£109,343	£859	£78	-0.092	0.006	£143,729	£12,994
Amgen NMA	£2,567	£1,786	-0.276	0.016	£156,113	£108,578	£837	£56	-0.091	0.006	£141,762	£9,432
Amgen STARs+NMA	£2,690	£1,909	-0.276	0.016	£163,599	£116,063	£861	£79	-0.091	0.006	£145,729	£13,399
No Naive util step	£2,548	£1,766	-0.288	0.015	£175,401	£121,589	£836	£54	-0.092	0.005	£162,929	£10,498
SCC ongoing mean	£2,548	£1,766	-0.288	0.020	£126,620	£87,774	£836	£54	-0.092	0.007	£120,980	£7,795
SCC ongoing max	£2,548	£1,766	-0.288	0.022	£113,410	£78,617	£836	£54	-0.092	0.008	£108,775	£7,008
No gen. mortality	£2,557	£1,772	-0.289	0.017	£146,781	£101,744	£839	£54	-0.093	0.006	£139,429	£9,057
5 yeat horizon	£2,548	£1,767	-0.286	0.017	£148,914	£103,282	£834	£54	-0.091	0.006	£141,622	£9,121
2 year horizon	£2,443	£1,698	-0.267	0.016	£156,692	£108,877	£781	£36	-0.083	0.005	£148,731	£6,827
vd Hout utility	£2,548	£1,766	-0.288	0.014	£177,567	£123,091	£836	£54	-0.092	0.005	£168,010	£10,825
SAE P1+	£2,548	£1,766	-0.288	0.014	£188,601	£130,740	£836	£54	-0.092	0.010	£87,426	£5,633
No SAE	£2,535	£1,747	-0.290	0.018	£139,278	£95,988	£834	£46	-0.093	0.006	£143,426	£7,867
No gen. discs.	£6,004	£4,173	-0.677	0.038	£157,753	£109,654	£1,619	-£211	-0.183	0.012	£138,680	Dominant
No discs.	£6,150	£4,275	-0.694	0.039	£158,204	£109,980	£1,686	-£189	-0.190	0.012	£139,541	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	£2,549	£1,767	-0.286	0.017	£147,049	£101,951	£838	£56	-0.090	0.006	£142,626	£9,591

OST+NSCLC NAIVE	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£2,473	£1,691	-0.343	0.024	£103,350	£70,679	£823	£41	-0.103	0.008	£106,812	£5,337
Amgen STARs	£2,618	£1,836	-0.343	0.024	£109,409	£76,737	£850	£68	-0.103	0.008	£110,310	£8,834
Amgen NMA	£2,509	£1,727	-0.320	0.022	£112,789	£77,644	£825	£43	-0.102	0.008	£108,515	£5,702
Amgen STARs+NMA	£2,646	£1,864	-0.320	0.022	£118,943	£83,798	£852	£70	-0.102	0.008	£111,992	£9,179
No Naive util step	£2,473	£1,691	-0.343	0.018	£135,660	£92,775	£823	£41	-0.103	0.006	£137,904	£6,890
SCC ongoing mean	£2,473	£1,691	-0.343	0.027	£90,853	£62,132	£823	£41	-0.103	0.009	£94,286	£4,711
SCC ongoing max	£2,473	£1,691	-0.343	0.030	£82,514	£56,429	£823	£41	-0.103	0.010	£85,870	£4,290
No gen. mortality	£2,481	£1,696	-0.344	0.024	£103,033	£70,452	£826	£42	-0.104	0.008	£106,469	£5,359
5 yeat horizon	£2,476	£1,695	-0.338	0.024	£105,289	£72,086	£823	£42	-0.101	0.008	£109,190	£5,606
2 year horizon	£2,385	£1,639	-0.311	0.021	£113,714	£78,167	£775	£29	-0.090	0.007	£118,569	£4,448
vd Hout utility	£2,473	£1,691	-0.343	0.020	£124,310	£85,013	£823	£41	-0.103	0.006	£127,857	£6,388
SAE P1+	£2,473	£1,691	-0.343	0.020	£122,918	£84,061	£823	£41	-0.103	0.011	£72,937	£3,644
No SAE	£2,459	£1,671	-0.345	0.025	£98,978	£67,269	£821	£33	-0.104	0.008	£108,627	£4,347
No gen. discs.	£5,895	£4,064	-0.760	0.049	£120,402	£83,010	£1,608	-£222	-0.194	0.014	£113,154	Dominant
No discs.	£6,040	£4,165	-0.777	0.050	£121,082	£83,502	£1,675	-£200	-0.202	0.015	£114,173	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	£2,475	£1,693	-0.339	0.024	£103,297	£70,666	£828	£46	-0.099	0.007	£110,506	£6,173

OST+NSCLC EXPER	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£2,620	£1,839	-0.235	0.011	£238,840	£167,587	£848	£66	-0.082	0.004	£196,114	£15,282
Amgen STARs	£2,731	£1,949	-0.235	0.011	£248,919	£177,666	£869	£87	-0.082	0.004	£200,948	£20,115
Amgen NMA	£2,624	£1,842	-0.234	0.011	£241,247	£169,366	£849	£68	-0.081	0.004	£198,534	£15,801
Amgen STARs+NMA	£2,734	£1,952	-0.234	0.011	£251,348	£179,467	£870	£88	-0.081	0.004	£203,338	£20,606
No Naive util step	..	..	..	..	..	..	..	..	..	..	..	..
SCC ongoing mean	£2,620	£1,839	-0.235	0.013	£196,905	£138,162	£848	£66	-0.082	0.005	£164,375	£12,808
SCC ongoing max	£2,620	£1,839	-0.235	0.015	£171,707	£120,482	£848	£66	-0.082	0.006	£144,789	£11,282
No gen. mortality	£2,630	£1,845	-0.236	0.011	£238,622	£167,434	£851	£67	-0.082	0.004	£195,987	£15,403
5 yeat horizon	£2,617	£1,836	-0.235	0.011	£238,875	£167,612	£845	£65	-0.082	0.004	£196,090	£15,025
2 year horizon	£2,499	£1,753	-0.224	0.010	£239,796	£168,258	£788	£42	-0.076	0.004	£195,766	£10,537
vd Hout utility	£2,620	£1,839	-0.235	0.009	£290,357	£203,735	£848	£66	-0.082	0.004	£237,589	£18,514
SAE P1+	£2,620	£1,839	-0.235	0.007	£365,867	£256,718	£848	£66	-0.082	0.008	£107,304	£8,361
No SAE	£2,607	£1,820	-0.237	0.012	£220,707	£154,020	£846	£58	-0.083	0.004	£204,488	£14,044
No gen. discs.	£6,109	£4,278	-0.598	0.028	£221,438	£155,082	£1,630	-£201	-0.172	0.009	£176,418	Dominant
No discs.	£6,256	£4,381	-0.614	0.028	£221,084	£154,830	£1,696	-£178	-0.179	0.010	£176,813	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	..	..	..	..	..	..	..	..	..	..	..	..

Univariate sensitivity analyses: NSCLC

LUNG	BSC	BSC	BSC	BSC	BSC	BSC	ZOL	ZOL	ZOL	ZOL	ZOL	ZOL
ALL PATIENTS	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc	Ex PAS	Inc PAS	SREs	QALYs	ICER ex	ICER inc
Base Case	£2,262	£1,583	-0.218	0.012	£191,412	£133,926	£708	£28	-0.076	0.005	£149,878	£5,972
Amgen STARs	£2,362	£1,683	-0.218	0.012	£199,870	£142,383	£727	£47	-0.076	0.005	£153,881	£9,976
Amgen NMA	£2,262	£1,583	-0.218	0.012	£191,412	£133,926	£708	£28	-0.076	0.005	£149,878	£5,972
Amgen STARs+NMA	£2,362	£1,683	-0.218	0.012	£199,870	£142,383	£727	£47	-0.076	0.005	£153,881	£9,976
No Naive util step	£2,262	£1,583	-0.218	0.010	£218,252	£152,705	£708	£28	-0.076	0.004	£172,919	£6,891
SCC ongoing mean	£2,262	£1,583	-0.218	0.013	£178,698	£125,030	£708	£28	-0.076	0.005	£141,287	£5,630
SCC ongoing max	£2,262	£1,583	-0.218	0.013	£169,299	£118,454	£708	£28	-0.076	0.005	£134,827	£5,373
No gen. mortality	£2,269	£1,587	-0.219	0.012	£191,156	£133,744	£710	£29	-0.076	0.005	£149,719	£6,022
5 year horizon	£2,262	£1,583	-0.218	0.012	£191,529	£134,010	£708	£28	-0.076	0.005	£149,985	£5,982
2 year horizon	£2,227	£1,560	-0.212	0.011	£196,245	£137,432	£691	£23	-0.073	0.004	£153,552	£5,156
vd Hout utility	£2,262	£1,583	-0.218	0.009	£247,875	£173,431	£708	£28	-0.076	0.004	£194,185	£7,738
SAE P1+	£2,262	£1,583	-0.218	0.010	£219,997	£153,926	£708	£28	-0.076	0.006	£112,981	£4,502
No SAE	£2,248	£1,564	-0.220	0.013	£179,389	£124,828	£704	£21	-0.076	0.005	£155,322	£4,534
No gen. discs.	£3,848	£2,700	-0.357	0.018	£208,396	£146,237	£1,038	-£110	-0.104	0.007	£159,202	Dominant
No discs.	£3,888	£2,728	-0.360	0.019	£208,716	£146,469	£1,056	-£103	-0.105	0.007	£160,025	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	..	..	..	..	..	..	..	..	..	..	..	..

LUNG NAIVE	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£2,257	£1,578	-0.228	0.014	£158,333	£110,671	£693	£13	-0.087	0.006	£112,617	£2,135
Amgen STARs	£2,359	£1,679	-0.228	0.014	£165,463	£117,801	£715	£36	-0.087	0.006	£116,272	£5,790
Amgen NMA	£2,257	£1,578	-0.228	0.014	£158,333	£110,671	£693	£13	-0.087	0.006	£112,617	£2,135
Amgen STARs+NMA	£2,359	£1,679	-0.228	0.014	£165,463	£117,801	£715	£36	-0.087	0.006	£116,272	£5,790
No Naive util step	£2,257	£1,578	-0.228	0.011	£199,936	£139,750	£693	£13	-0.087	0.005	£142,333	£2,698
SCC ongoing mean	£2,257	£1,578	-0.228	0.015	£149,443	£104,457	£693	£13	-0.087	0.006	£107,042	£2,029
SCC ongoing max	£2,257	£1,578	-0.228	0.016	£142,745	£99,775	£693	£13	-0.087	0.007	£102,788	£1,948
No gen. mortality	£2,263	£1,582	-0.228	0.014	£158,064	£110,477	£695	£13	-0.088	0.006	£112,470	£2,170
5 year horizon	£2,257	£1,578	-0.227	0.014	£158,499	£110,792	£693	£13	-0.087	0.006	£112,748	£2,151
2 year horizon	£2,227	£1,559	-0.218	0.013	£165,275	£115,737	£678	£10	-0.083	0.006	£117,203	£1,790
vd Hout utility	£2,257	£1,578	-0.228	0.011	£205,154	£143,397	£693	£13	-0.087	0.005	£145,941	£2,766
SAE P1+	£2,257	£1,578	-0.228	0.013	£177,449	£124,032	£693	£13	-0.087	0.008	£90,041	£1,707
No SAE	£2,243	£1,559	-0.229	0.015	£149,896	£104,205	£689	£6	-0.088	0.006	£115,624	£947
No gen. discs.	£3,885	£2,737	-0.343	0.020	£191,622	£135,008	£1,029	-£119	-0.112	0.008	£128,843	Dominant
No discs.	£3,926	£2,766	-0.346	0.020	£192,291	£135,497	£1,048	-£112	-0.113	0.008	£129,997	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	..	..	..	..	..	..	..	..	..	..	..	..

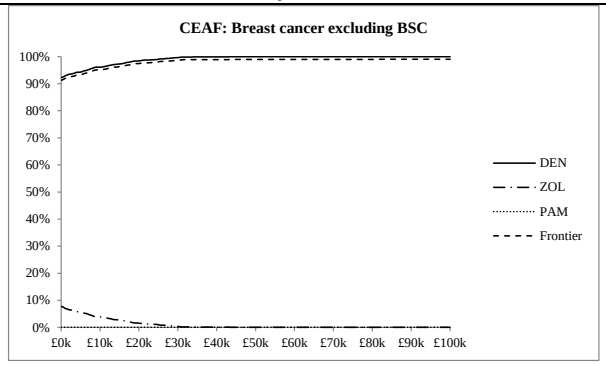
LUNG EXPER	BSC Ex PAS	BSC Inc PAS	BSC SREs	BSC QALYs	BSC ICER ex	BSC ICER inc	ZOL Ex PAS	ZOL Inc PAS	ZOL SREs	ZOL QALYs	ZOL ICER ex	ZOL ICER inc
Base Case	£2,268	£1,588	-0.210	0.009	£239,211	£167,529	£722	£43	-0.065	0.003	£215,614	£12,743
Amgen STARs	£2,366	£1,686	-0.210	0.009	£249,586	£177,905	£738	£58	-0.065	0.003	£220,231	£17,361
Amgen NMA	£2,268	£1,588	-0.210	0.009	£239,211	£167,529	£722	£43	-0.065	0.003	£215,614	£12,743
Amgen STARs+NMA	£2,366	£1,686	-0.210	0.009	£249,586	£177,905	£738	£58	-0.065	0.003	£220,231	£17,361
No Naive util step	..	..	..	..	..	..	..	..	..	..	..	..
SCC ongoing mean	£2,268	£1,588	-0.210	0.010	£219,862	£153,979	£722	£43	-0.065	0.004	£200,348	£11,841
SCC ongoing max	£2,268	£1,588	-0.210	0.011	£205,940	£144,229	£722	£43	-0.065	0.004	£189,156	£11,180
No gen. mortality	£2,274	£1,593	-0.210	0.010	£239,011	£167,390	£725	£43	-0.065	0.003	£215,469	£12,821
5 year horizon	£2,267	£1,588	-0.210	0.009	£239,211	£167,529	£722	£43	-0.065	0.003	£215,613	£12,735
2 year horizon	£2,227	£1,560	-0.206	0.009	£239,322	£167,607	£703	£36	-0.063	0.003	£215,451	£10,888
vd Hout utility	£2,268	£1,588	-0.210	0.007	£309,520	£216,770	£722	£43	-0.065	0.003	£279,244	£16,504
SAE P1+	£2,268	£1,588	-0.210	0.008	£285,459	£199,919	£722	£43	-0.065	0.005	£147,641	£8,726
No SAE	£2,253	£1,569	-0.211	0.010	£220,987	£153,914	£719	£35	-0.065	0.003	£227,229	£11,032
No gen. discs.	£3,813	£2,665	-0.370	0.017	£227,929	£159,313	£1,046	-£102	-0.096	0.005	£204,827	Dominant
No discs.	£3,851	£2,692	-0.374	0.017	£227,770	£159,197	£1,064	-£96	-0.097	0.005	£204,801	Dominant
TTF form AG naive	..	..	..	..	..	..	..	..	..	..	..	..
TTF form AG all	..	..	..	..	..	..	..	..	..	..	..	..

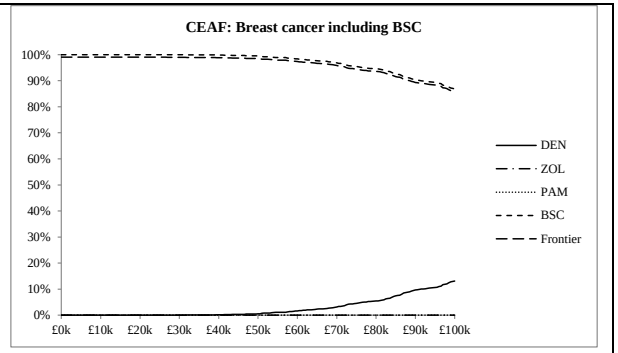
Probabilistic modelling: All patients pooled HRs and RRs across SRE naïve and SRE experienced with PAS

BRST	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.822	[redacted]	0.028	£4,269	£154,944
ZOL	1.842		0.007	-£243	Dominant
DEN	1.849		..	..	..
PAM	1.840		0.010	-£3,246	Dominant

WTP/Q	DEN	ZOL	PAM
£0k	92%	8%	0%
£20k	98%	2%	0%
£30k	100%	0%	0%
£40k	100%	0%	0%
£100k	100%	0%	0%

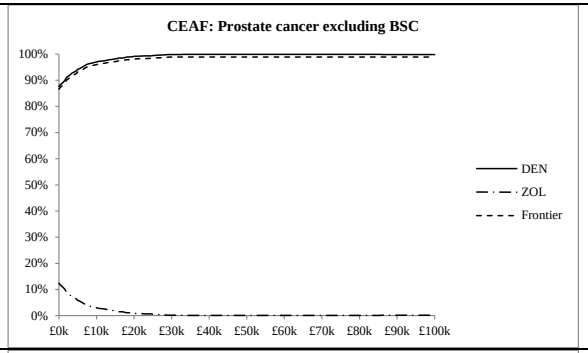
WTP/Q	DEN	ZOL	PAM	BSC
£0k	0%	0%	0%	100%
£20k	0%	0%	0%	100%
£30k	0%	0%	0%	100%
£40k	0%	0%	0%	100%
£100k	13%	0%	0%	87%

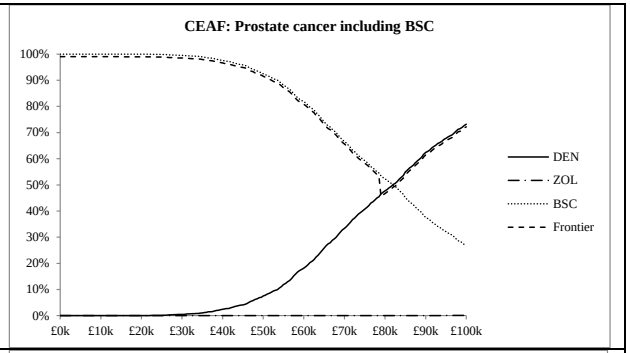




PROS	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.065	[redacted]	0.035	£2,764	£78,756
ZOL	1.091		0.009	-£123	Dominant
DEN	1.100		..	..	..

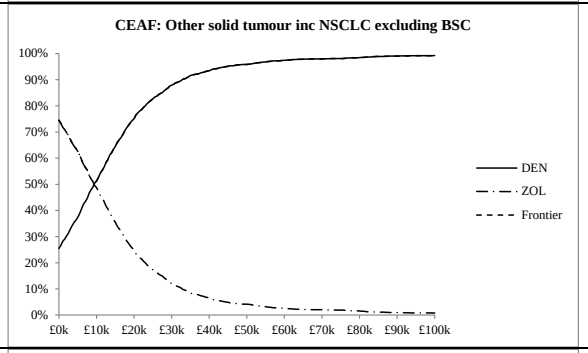
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	88%	12%	0%	0%	100%
£20k	99%	1%	0%	0%	100%
£30k	100%	0%	0%	0%	100%
£40k	100%	0%	2%	0%	98%
£100k	100%	0%	73%	0%	27%

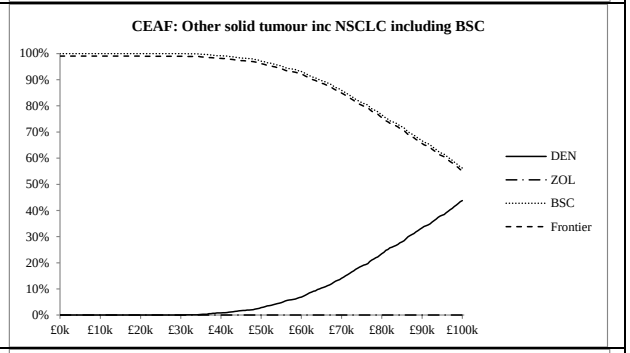




OSTL	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.701	[redacted]	0.017	£1,771	£102,102
ZOL	0.713		0.006	£56	£9,391
DEN	0.719		..	..	..

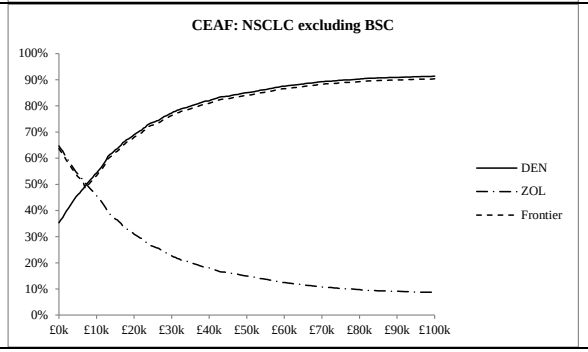
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	26%	75%	0%	0%	100%
£20k	75%	25%	0%	0%	100%
£30k	88%	12%	0%	0%	100%
£40k	93%	7%	1%	0%	99%
£100k	99%	1%	44%	0%	56%

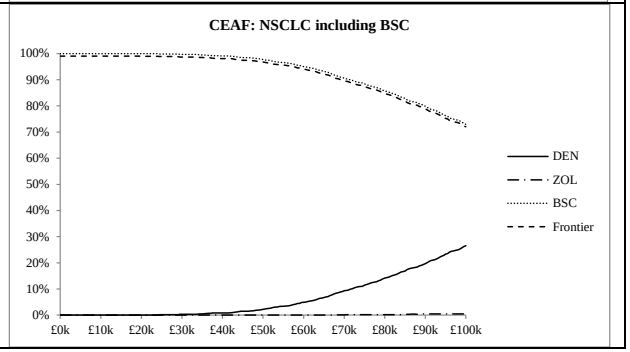




LUNG	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.439	[redacted]	0.012	£1,582	£132,177
ZOL	0.446		0.005	£32	£6,967
DEN	0.451		..	..	..

WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	35%	65%	0%	0%	100%
£20k	69%	31%	0%	0%	100%
£30k	77%	23%	0%	0%	100%
£40k	82%	18%	1%	0%	99%
£100k	91	9%	27%	1%	73%



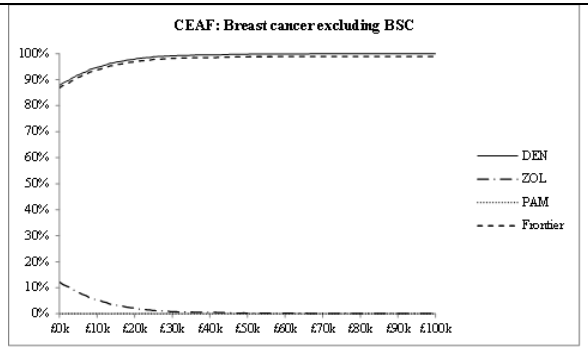


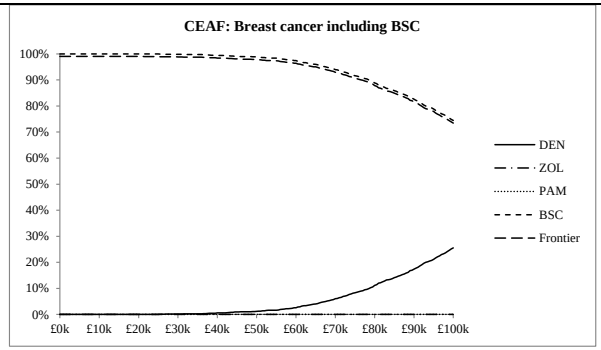
SRE Naive patients

BRST	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.848	[redacted]	0.035	£4,340	£124,461
ZOL	1.875		0.008	-£204	Dominant
DEN	1.883		..	..	..
PAM	1.873		0.009	£3,109	Dominant

WTP/Q	DEN	ZOL	PAM
£[illegible]k	88%	12%	0%
£20k	98%	2%	0%
£30k	99%	1%	0%
£40k	99%	1%	0%
£100k	100%	0%	0%

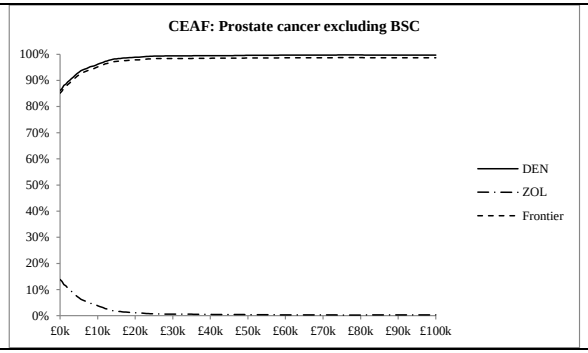
WTP/Q	DEN	ZOL	PAM	BSC
£0k	0%	0%	0%	100%
£20k	0%	0%	0%	100%
£30k	0%	0%	0%	100%
£40k	1%	0%	0%	99%
£100k	26%	0%	0%	74%

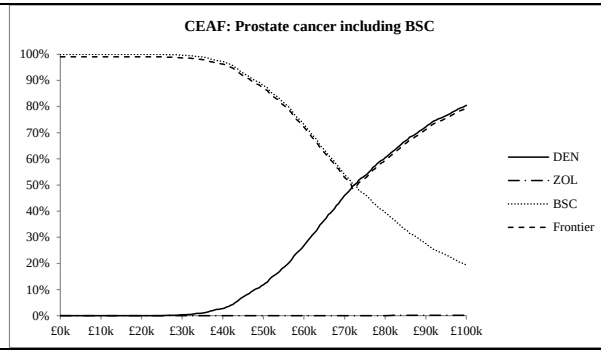




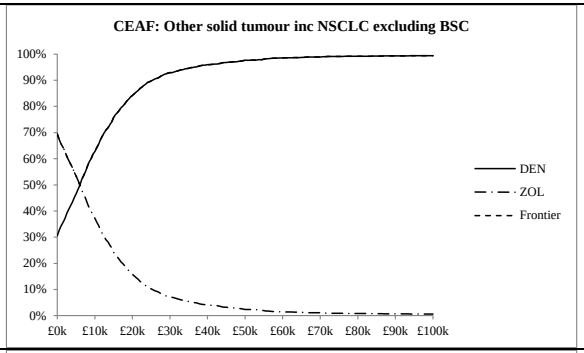
PROS	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.088	[redacted]	0.039	£2,786	£71,920
ZOL	1.116		0.011	-£121	Dominant
DEN	1.126		..	..	..

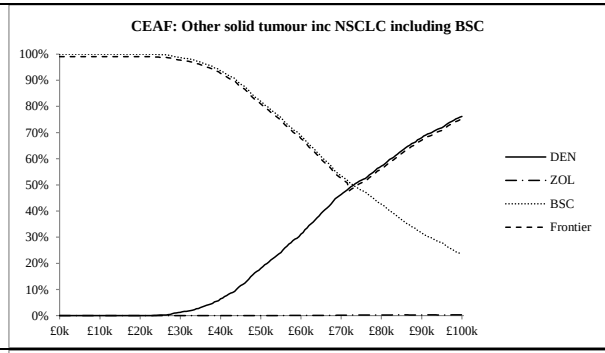
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	86%	14%	0%	0%	100%
£20k	99%	1%	0%	0%	100%
£30k	99%	1%	0%	0%	100%
£40k	99%	1%	3%	0%	97%
£100k	100%	0%	81%	0%	19%



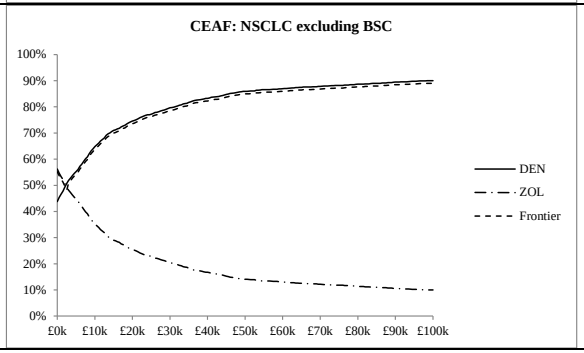


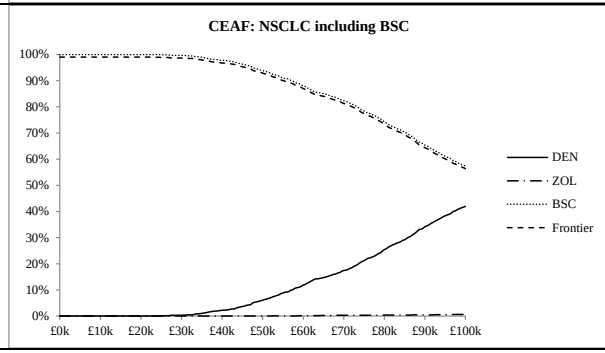
OSTL	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.715	[redacted]	0.024	£1,702	£71,883
ZOL	0.731		0.008	£45	£5,848
DEN	0.739		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	31%	69%	0%	0%	100%
£20k	84%	16%	0%	0%	100%
£30k	93%	7%	1%	0%	99%
£40k	96%	4%	6%	0%	94%
£100k	99%	1%	76%	0%	24%





LUNG	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.453	[redacted]	0.014	£1,578	£109,934
ZOL	0.461		0.006	£16	£2,620
DEN	0.467		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	44%	56%	0%	0%	100%
£20k	75%	25%	0%	0%	100%
£30k	80%	20%	0%	0%	10□%
£40k	83%	17%	2%	0%	98%
£100k	90%	10%	42%	1%	57%



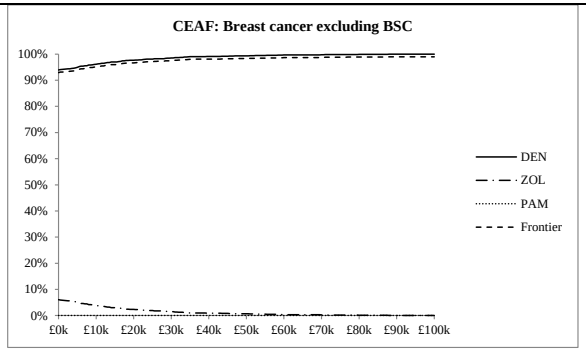


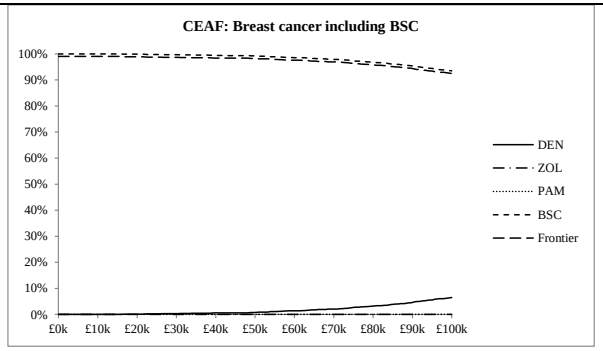
SRE Experienced patients

BRST	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	1.778	[redacted]	0.017	£4,146	£241,181
ZOL	1.790		0.005	-£298	Dominant
DEN	1.795		..	..	..
PAM	1.785		0.0?0	£3,470	Dominant

WTP/Q	DEN	ZOL	PAM
£0k	94%	6%	0%
£20k	98%	2%	0%
£30k	99%	1%	0%
£40k	99%	1%	0%
£100k	100%	0%	0%

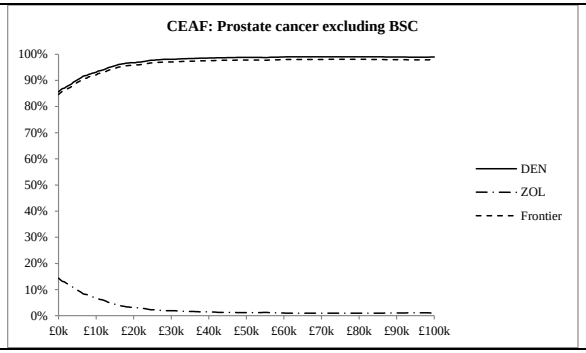
WTP/Q	DEN	ZOL	PAM	BSC
£0k	0%	0%	0%	100%
£20k	0%	0%	0%	100%
£30k	0%	0%	0%	100%
£40k	1%	0%	0%	99%
£100k	7%	0%	0%	94%

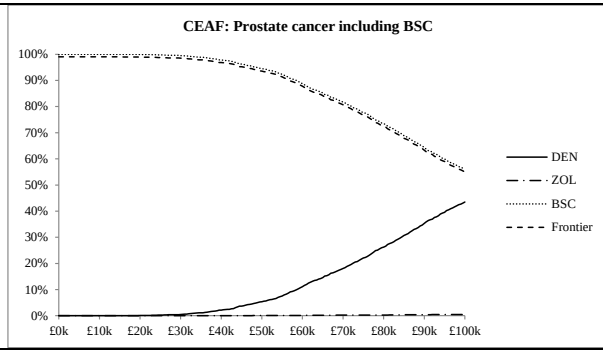




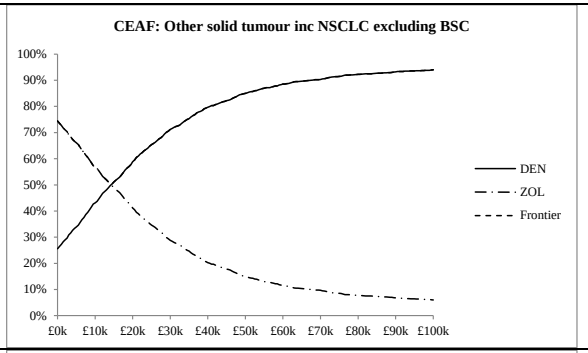
PROS	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.996	[redacted]	0.027	£2,695	£101,216
ZOL	1.017		0.006	-£132	Dominant
DEN	1.023		..	..	..

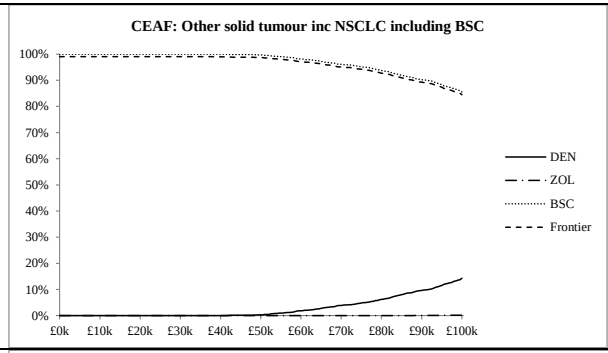
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	86%	14%	0%	0%	100%
£20k	97%	3%	0%	0%	100%
£30k	98%	2%	1%	0%	100%
£40k	99%	1%	2%	0%	98%
£100k	99%	1%	44%	1%	56%





OSTL	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.689	[redacted]	0.011	£1,825	£159,757
ZOL	0.696		0.004	£63	£14,373
DEN	0.700		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	26%	74%	0%	0%	100%
£20k	59%	41%	0%	0%	100%
£30k	71%	29%	0%	0%	100%
£40k	80%	20%	0%	0%	100%
£100k	94%	6%	14%	0%	86%





LUNG	QALY	£ Total	Δ QALY	Δ Cost	ICER
BSC	0.425	[redacted]	0.010	£1,572	£157,231
ZOL	0.432		0.003	£41	£12,415
DEN	0.435		..	..	..
WTP/Q	DEN	ZOL	DEN	ZOL	BSC
£0k	33%	67%	0%	0%	100%
£20k	59%	41%	0%	0%	100%
£30k	66%	34%	0%	0%	100%
£40k	72%	28%	1%	0%	99%
£100k	84%	16%	20%	1%	79%