Evidence Review Group Report

Aflibercept in combination with irinotecan and fluorouracil-based therapy for the treatment of metastatic colorectal cancer which has progressed following prior oxaliplatin-based chemotherapy

Erratum

Page 14, first paragraph

The text: "in the UK between 2007 and 2009, an average 72% of colorectal cancer cases were diagnosed in people aged 65 years and over, whilst in the trial only 33.5% of the aflibercept group and 38.9% of the placebo group were aged over 65 years; the proportion of patients in the trial with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 (2.2%) was lower than seen in other second-line clinical trials and standard UK practice; and the proportion of patients who had metastatic involvement of only one organ was higher in the trial population than in patients seen in standard UK practice. Subgroup analyses suggest that patients with less advanced disease (ECOG PS 0, number of organs with metastases 1 or less, and liver only metastases) may be more likely to benefit from aflibercept, although there was no statistically significant interaction."

Should read: "in the UK between 2007 and 2009, an average 72% of colorectal cancer cases were diagnosed in people aged 65 years and over, whilst in the trial only 33.5% of the aflibercept group and 38.9% of the placebo group were aged over 65 years; the proportion of patients in the trial with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 (2.2%) was lower than seen in other second-line clinical trials and standard UK practice; and the proportion of patients who had metastatic involvement of only one organ was, according to our clinical advisor, higher in the trial population than in patients seen in standard UK practice. Subgroup analyses suggest that patients with less advanced disease (ECOG PS 0, number of organs with metastases 1 or less) may be more likely to benefit from aflibercept, although there was no statistically significant interaction."

Page 15, end of last paragraph

The text: "Implicitly the use of independent parametric functions resulted in an increasing hazard ratio of OS over time. That is, the relative effectiveness measure applied vs. FOLFIRI alone was more favourable as the time horizon increased."

Should read: "The use of the independent parametric functions resulted in the hazard ratio decreasing from HR>1 to HR<1 over the first year and then increasing slowly over the time frame of the model without ever returning to 1. That is, the relative treatment effect increases until ~12 months after which it begins to decrease (i.e. the survival curves begin to converge). However, the relative treatment estimate declines at a relatively slow rate over the remaining time horizon of the model and importantly suggests a continuing treatment effect on OS during the entire 15 year horizon."

Page 16, last paragraph

The text:" The extrapolation was based on a small numbers of patients still at risk past 30 months, making the extrapolation and the difference in OS uncertain."

Should read: "The extrapolation was based on a population with a small number of patients still at risk past 30 months, and there is considerable uncertainty to the extrapolation and difference in OS beyond the observed period."

The text: "The ERG also identified several errors and other areas of concern with the model. Firstly, the acquisition and administration costs were not related to the proportion of patients on treatment in the model."

Should read: "The ERG also identified other areas of concern with the model. Firstly, the acquisition and administration costs were not applied to all patients in the second line treatment health state of the model."

Page 17, 3rd paragraph

The text: "There were very small numbers of patients at risk in the OS analysis at the later time points, which reduces the reliability of the longer-term results"

Should read: "There were very small numbers of patients at risk in the OS analysis at the later time points. The small portion of patients at risk compared to the number of patients censored increases the uncertainty surrounding the longer-term results."

The text: "There were no HRQoL data presented in the clinical section of the MS"

Should read: "There were no HRQoL data collected in the VELOUR trial"

Page 18, 1st paragraph

The text: "The ERG explored two assumptions other than the manufacturer's base case which assumed that the treatment effect of aflibercept increased over time."

Should read: "The ERG explored two assumptions other than the manufacturer's base case which assumed that the treatment effect of aflibercept continued for the full time horizon of the model."

Page 20, 4th paragraph

The text: "There were no HRQoL data presented in the clinical section of the MS"

Should read: "There were no HRQoL data collected in the VELOUR trial"

Page 29, 3rd paragraph

The text: “Further, the MeSH terms used (‘Colorectal Neoplasms’, ‘Colonic Neoplasms’ and ‘Rectal Neoplasms’) were not exploded, and so additional MeSH terms found further down the MeSH hierarchy would not have been searched for.” has been deleted.

Page 35, 2nd paragraph

The text: “The MS contains a *post-hoc* subgroup analysis, excluding patients who received oxaliplatin as adjuvant therapy.”

Should read: “The MS contains a *post-hoc* subgroup analysis, excluding patients who progressed on or within 6 months of oxaliplatin-based adjuvant therapy."

Page 35, 4th paragraph

The text: In the UK between 2007 and 2009, an average 72% of colorectal cancer cases were diagnosed in people aged 65 years and over,[28] whilst in the trial only 33.5% of the aflibercept group and 38.9% of the placebo group were aged over 65 years. Therefore, the patients included in the trial were younger than those seen in standard UK practice. In addition, the ERG clinical advisor stated that the proportion of patients in the trial with an ECOG PS of 2 (2.2%) was lower than seen in other second-line clinical trials[29] and standard UK practice, and that the proportion of patients who had metastatic involvement of only one organ (42-44% of the trial population) was also higher in the trial population than in patients seen in standard UK practice.”

Should read: “In the UK between 2007 and 2009, an average 72% of colorectal cancer cases were diagnosed in people aged 65 years and over,[28] whilst in the trial only 33.5% of the aflibercept group and 38.9% of the placebo group were aged over 65 years. Therefore, the patients included in the trial may have been younger than those seen in standard UK practice. In addition, the ERG clinical advisor stated that the proportion of patients in the trial with an ECOG PS of 2 (2.2%) was lower than seen in other second-line clinical trials[29] and standard UK practice, and he also advised that the proportion of patients who had metastatic involvement of only one organ (42-44% of the trial population) was also higher in the trial population than in patients seen in standard UK practice. “

Page 40, 3rd paragraph

The text: “The survival curves (presented in Figure 4.1) do not suggest that median survival is inappropriate to use in the economic analysis.” should be deleted.

Page 40, 6th paragraph

The text: "The mean OS benefit estimate varies considerably (from 3 months to [redacted] months) depending on which distribution is used, which indicates that the mean OS results presented may not be reliable."

Should read: “The mean OS benefit estimate varies considerably (from 3 months to [redacted] months) depending on which distribution is used, which indicates that the mean OS results presented are not robust to the choice of distribution and there is a high degree of uncertainty surrounding the mean OS results.”

Page 45, 2nd paragraph

The text: "The time periods used to calculate hazard ratios were unequal as all time points beyond 18 months were combined, making the HR unreliable for this time point."

Should read: “The time periods used to calculate hazard ratios were unequal as all time points beyond 18 months were combined.”

Page 47, 2nd paragraph

The text: "The mean OS estimate varies considerably, depending on which distribution is used, which indicates that the mean OS results presented may not be reliable."

Should read: “The mean OS estimate varies considerably, depending on which distribution is used, which indicates that the mean OS results presented are not robust to the choice of distribution and there is a high degree of uncertainty surrounding the mean OS results.”

Page 50, 1st paragraph

The text: “By using mean survival, rather than median survival, the few patients with long term survival have greater weight in the analysis. The survival curves presented in Figure 4.1 do not suggest that median survival is inappropriate to use in the economic analysis.”

Should read: “By using mean survival, rather than median survival, the few patients with long term survival have greater weight in the analysis.”

Page 50, 3rd paragraph

The text: “Whilst there was no evidence of a significant interaction between treatment groups for most of the baseline patient characteristics, the results suggest that patients with less advanced disease (ECOG PS 0, number of organs with metastases ≤ 1, liver only metastases) may be more likely to benefit from aflibercept. However, differences in characteristics between trial participants and patients seen in standard UK practice suggest that patients in the VELOUR trial are likely to be fitter than patients eligible for aflibercept plus FOLFIRI in practice; patients seen in practice are more likely to have more than one site of metastatic disease, to be older and have a worse ECOG PS than patients in the VELOUR trial.”

Should read: “Whilst there was no evidence of a significant interaction between treatment groups for most of the baseline patient characteristics, the results suggest that patients with less advanced disease (ECOG PS 0, number of organs with metastases ≤ 1) may be more likely to benefit from aflibercept. However, differences in characteristics between trial participants and patients seen in standard UK practice suggest that patients in the VELOUR trial are likely to be fitter than patients eligible for aflibercept plus FOLFIRI in practice; the

ERG clinical advisor stated that patients seen in practice are more likely to have more than one site of metastatic disease, to be older and have a worse ECOG PS than patients in the VELOUR trial."

Page 54, last paragraph

The text: "Table B15 of the MS (presented as Table 4.8 below) presents the most frequent adverse events (incidence ≥20% or ≥5% higher in the aflibercept arm), other anti-VEGF-associated events, and most frequent biologic abnormalities. With the exception of nausea, vomiting, alopecia, constipation, and the anti-VEGF-associated events 'fistula from other than GI origin' and GI perforation, which were similar between groups, all other adverse events were more common in the aflibercept group; particularly grade 3 diarrhoea, grade 3 hypertension, and all grades of: stomatitis and ulceration, infections and infestations, hypertension, haemorrhage, epistaxis, dysphonia, headache, proteinuria."

Should read: "Table B15 of the MS (presented as Table 4.8 below) presents the most frequent adverse events (incidence ≥20% or ≥5% higher in the aflibercept arm), other anti-VEGF-associated events, and most frequent biologic abnormalities. With the exception of anaemia, which was more common in the placebo group; and nausea, vomiting, alopecia, constipation, and the anti-VEGF-associated events 'fistula from other than GI origin' and GI perforation, which were similar between groups, all other adverse events were more common in the aflibercept group; particularly grade 3 diarrhoea, grade 3 hypertension, and all grades of: stomatitis and ulceration, infections and infestations, hypertension, haemorrhage, epistaxis, dysphonia, headache, proteinuria."

Page 59, 2nd paragraph

The text: The VELOUR trial was conducted in 28 countries; only 99 of the 1,226 participants were from the UK. The demographic and disease characteristics of the trial participants suggest that they were potentially younger and healthier than the population eligible for aflibercept plus FOLFIRI in UK practice. Subgroup analyses suggest that patients with less advanced disease (ECOG PS 0, number of organs with metastases 1 or less, and liver only metastases) may be more likely to benefit from aflibercept, although there was no statistically significant interaction."

Should read: "The VELOUR trial was conducted in 28 countries; only 99 of the 1,226 participants were from the UK. The demographic and disease characteristics of the trial participants suggest that they were potentially younger and healthier than the population eligible for aflibercept plus FOLFIRI in UK practice, according to the ERG clinical advisor. Subgroup analyses suggest that patients with less advanced disease (ECOG PS 0, number of organs with metastases 1 or less) may be more likely to benefit from aflibercept, although there was no statistically significant interaction."

Page 74, 1st paragraph

The text: "In the UK between 2007 and 2009, an average 72% of colorectal cancer cases were diagnosed in people aged 65 years and over, whilst in the trial only 33.5% of the aflibercept group and 38.9% of the placebo group were aged over 65 years; the proportion of patients in the trial with an ECOG PS of 2 (2.2%) was, according to our clinical advisor, lower than seen in standard UK practice; and the proportion of patients who had only one primary site was higher in the trial population than in patients seen in standard UK practice. Furthermore, in the UK the median age of mCRC patients at diagnosis has been estimated to be 70 years[10], whereas the median age at baseline in the VELOUR trial was 61.0 for both treatment arms. Subgroup analyses suggest that patients with less advanced disease (ECOG PS 0, number of organs with metastases 1 or less, and liver only metastases) may be more likely to benefit from aflibercept, although there was no statistically significant interaction."

Should read: "In the UK between 2007 and 2009, an average 72% of colorectal cancer cases were diagnosed in people aged 65 years and over, whilst in the trial only 33.5% of the aflibercept group and 38.9% of the placebo group were aged over 65 years; the proportion of patients in the trial with an ECOG PS of 2 (2.2%) was, according to our clinical advisor, lower than seen in standard UK practice; and the proportion of patients who had only one primary site was higher in the trial population than in patients seen in standard UK practice, according to our clinical advisor. Furthermore, in the UK the median age of mCRC patients at diagnosis has been estimated to be 70 years[10], whereas the median age at baseline in the VELOUR trial was 61.0 for both treatment arms. Subgroup analyses suggest that patients with less advanced disease (ECOG PS 0, number of organs with metastases 1 or less) may be more likely to benefit from aflibercept, although there was no statistically significant interaction."

Page 76, last paragraph

The text: "The manufacturer's base case assumption that the HR decreases over time suggests that not only is there a continued treatment effect, but that the treatment effect actually improves over time. "

Should read: "The use of the independent parametric functions resulted in the hazard ratio decreasing from HR>1 to HR<1 over the first year and then increasing slowly over the time frame of the model without ever returning to 1. That is, the relative treatment effect increases until ~12 months after which it begins to decrease (i.e. the survival curves begin to converge). However, the relative treatment estimate declines at a relatively slow rate over the remaining time horizon of the model and importantly suggests a continuing treatment effect on OS during the entire 15 year horizon."

Page 77, 1st paragraph

The text: "The assumption that the OS curves continue to diverge during the extrapolation period appears contrary to the PFS data from VELOUR that show that after approximately

one year the PFS curves converge: there is no treatment difference after about 12 months (Figure 4.4)."

Should read: "The assumption that the OS curves do not fully converge during the extrapolation period appears contrary to the PFS data from VELOUR that show that after approximately one year the PFS curves converge: there is no treatment difference after about 12 months (Figure 4.4)."

Page 77, 3rd paragraph

The text: "As described previously in section 4.2.3, there is high uncertainty around the OS survival estimates past 30 months due to the small number of patients at risk (n=10 and n=6 for aflibercept + FOLFIRI and FOLFIRI respectively) at 33 months and (n=1 and n=0 for aflibercept + FOLFIRI and FOLFIRI respectively) at 36 months."

Should read: "As described previously in section 4.2.3, there is high uncertainty around the OS survival estimates past 30 months due to the amount of censoring (209 for aflibercept + FOLFIRI and 154 for FOLFIRI) and the small number of patients at risk (n=10 and n=6 for aflibercept + FOLFIRI and FOLFIRI respectively) at 33 months and (n=1 and n=0 for aflibercept + FOLFIRI and FOLFIRI respectively) at 36 months."

Page 83, 1st paragraph

The text: "The manufacturer argued that the sample of society from which the UK norms were derived included a significant proportion of individuals reporting disability (higher than in other national surveys)."

Should read: "The manufacturer reported that the sample of society from which the UK norms were derived included a significant proportion of individuals reporting disability (higher than in other national surveys)."

Page 86, 2nd paragraph

The text: "Hence, the apparent robustness of the model results to disutility of AEs may also be in part attributed to this error."

Should read: "Hence, the apparent robustness of the model results to changes in the absolute disutility values for each type of AE may also be in part attributed to this error. Repeating the analysis that simultaneously doubled disutility estimates for each type of AE on the corrected model increased the base case ICER by 9.05%."

Page 98, 2nd paragraph

The text: "The assumptions for the subgroup specific base cases were not described in the MS."

Should read: "The assumptions for the subgroup specific base cases were described in Appendix 14."

Page 103

Figure 5.4 and associated text should be marked CIC.

Page 109, 2nd paragraph

The text: “By fitting separate parametric curves to each treatment arm, it was assumed in the MS that the relative treatment effect on OS will continue to increase over the extrapolation period. That is, the OS curves continue to diverge during this period.”

Should read: “By fitting separate parametric curves to each treatment arm, it was assumed in the MS that the relative treatment effect on OS will not fully converge over the extrapolation period. That is, the model assumes a continuing treatment effect on OS during the entire 15 year horizon.”

Page 111, 1st paragraph

The text: “Since the treatment effect may not continue increasing for the entire duration of the model time horizon (…) ii) the difference in the treatment effect for OS declines over 12 or 18 months until there are no differences in the treatment arms (i.e. allowing for the curves to converge at an earlier point).”

Should read: “Since the treatment effect may not continue for the entire duration of the model time horizon (…) ii) the difference in the treatment effect for OS declines over 12 or 18 months until there are no differences in the treatment arms (i.e. allowing for the curves to fully converge at an earlier time point).”