CASE AUTH/2705/3/14

ROCHE v MERCK SERONO

Presentation of Erbitux clinical trials results in a press release

Roche complained about the way in which Merck Serono represented the results of the FIRE-3 AIO (Arbeitgemeinschaft Internistische Onkologie) clinical trial in a UK press release issued 28 September 2013 and also raised concerns about such data in unidentified Erbitux (cetuximab) promotional materials.

At that time Erbitux was indicated, *inter alia*, for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer (mCRC) in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX (folinic acid, fluorouracil and oxiplatin), and as a single agent in patients who had failed oxaliplatin and irinotecan-based therapy and who were intolerant to irinotecan.

Roche marketed Avastin (bevacizumab) which was indicated, *inter alia*, in combination with fluoropyrimidine-based chemotherapy for the treatment of adult patients with metastatic carcinoma of the colon or rectum.

The detailed response from Merck Serono is given below.

Roche explained that the FIRE-3 study trial evaluated the superiority of cetuximab plus combination chemotherapy, compared with bevacizumab plus combination chemotherapy in the first-line treatment of KRAS wild-type mCRC. The primary endpoint for the study was overall response rate. Secondary endpoints included progression-free survival and overall survival. Importantly it was not a treatment sequencing study as subsequent lines of treatment were not specified.

Roche stated that the primary analysis of the study, presented at the American Society of Clinical Oncology (ASCO) 2013, showed that the study failed to reach its primary endpoint. There was no significant difference in overall response rate (primary endpoint) between the two treatment arms. There was also no significant difference in progression-free survival between the two arms, but increased overall survival in the arm receiving cetuximab plus chemotherapy as first-line treatment (one of the secondary endpoints) was reported. The Kaplan-Meier curves of overall survival presented at ASCO 2013 showed that the lines, representing the different study arms, did not begin to separate until the 15-18 month time point. Given that the median time to first progression was approximately 10 months in both arms and the reported median duration of first-line treatment was significantly shorter than this in both arms, there would appear to be significant grounds to question the degree to which the first-line treatment was responsible for any overall survival difference demonstrated.

Roche noted that a second FIRE-3 analysis presented in July 2013 at the World Congress on Gastrointestinal Cancer, provided details of the second-line treatments administered to patients in the FIRE-3 trial. This analysis showed differences in the treatments received in the second-line setting by patients in the two arms. A further FIRE-3 analysis presented at the European Society for Medical Oncology (ESMO) European Cancer Congress (ECC), October 2013, showed the results of a pre-planned exploratory analysis of a sub-group of patients who were not only KRAS wild-type, but also NRAS wild-type (termed RAS wild-type). In that new sub-group of patients, the first-line cetuximab plus chemotherapy arm again failed to show a significant improvement over the bevacizumab plus chemotherapy arm in both overall response rate and progression free survival. However, the analysis showed a difference of 7.5 months in median overall survival between the two arms in favour of the group receiving cetuximab plus chemotherapy as their first-line regimen. As for the previous KRAS overall survival analysis, the Kaplan-Meier curves did not separate until well after completion of first-line treatments and first progression.

Merck Serono's press release about the FIRE-3 trial analysis after the ESMO-ECC congress was headed: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'. Roche stated that the press release was the source material for at least one article in the medical press and similar messages were used in promotional materials in Ireland (with prescribing information stating it was for UK and Ireland) but was not sure if it was being used in the UK.

Roche alleged that the overall survival statement in the heading 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study' was misleading because the FIRE-3 study failed to reach its primary endpoint of overall response rate. The heading was based on a sub-group analysis from this 'negative' phase III study. The fact that the study did not meet its primary endpoint was not prominently presented in the press release; it was only mentioned midway down the second page. Roche alleged a breach. Findings from secondary endpoints must be set within the context of the primary endpoints companies could not 'cherry pick' favourable findings.

The Panel noted that the press release was dated 28 September 2013 and thus the relevant Code was the Second 2012 Edition (amended) Code.

The Panel noted that the press release was headed 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study', below the heading in slightly smaller text were two bullet points; 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 to 33.1 months (p=0.011) in mCRC patients with RAS wild-type tumours receiving 1st line Erbitux plus FOLFIRI compared with patients receiving bevacizumab plus FOLFIRI' and 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'.

Text beneath referred to the phase III head-to-head trial which showed a 'clinically relevant improvement from Erbitux (cetuximab) plus FOLFIRI vs bevacizumab plus FOLFIRI as first-line treatment in metastatic colorectal cancer (mCRC) in patients with RAS wild-type tumours'.

The Panel noted that the FIRE-3 study was a multicentre randomised phase III trial investigating 5-FU, folinic acid and irinotecan (FOLFIRI) plus cetuximab vs FOLFIRI plus bevacizumab in first-line treatment of mCRC. The study failed to meet its primary endpoint of overall response rate (ORR). Secondary endpoints included median progression free survival (PFS) and median overall survival.

The summary of the FIRE-3 study principal investigator's presentation at the European Cancer Congress stated 'OS was markedly superior (Δ = 7.5 months, HR 0.70) in all RAS wild-type patients receiving first-line therapy with cetuximab (p=0.011)'. The presentation concluded that upfront determination of RAS (KRAS and NRAS) mutation status appeared to be highly recommendable in patients with metastatic disease and concluded that 'Patients with all-RAS wild-type tumours have a clinically relevant survival benefit when first-line treatment with cetuximab is offered'.

The Panel disagreed with Merck Serono's decision that as the lack of difference in ORR and PFS had previously been reported in the ASCO press release and as there was no change in these endpoints it was not considered appropriate to include them in the heading. The Panel considered that the heading, 'Merck Serono's Erbitux Significantly Extends Survival to 7.5 Months in mCRC Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study', was not a fair reflection of the overall data; it had not been placed within context of the study's primary outcome. The reference to the study's failure to meet its primary endpoint of objective response rate based on investigators' read in patients with KRAS EXON 2 wild-type tumours appeared in the third paragraph on page 2 and was insufficient to counter the heading. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the secondary endpoint findings. The heading was therefore misleading as alleged and the Panel ruled a breach of the Code. This ruling was upheld on appeal by Merck Serono.

Roche stated that the first bullet point: 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 months to 33.1 months (p=0.011) …' was the result of a sub-group analysis from the negative phase III study. Further contextualisation outlined in the background section was critical for the audience to be able to understand the clinical relevance. The press release failed to set the finding clearly in the context of the overall study which failed to meet its primary endpoint. In addition, the word 'exploratory' was only used much later in the press release to describe that analysis. Roche alleged that this rendered the press release misleading.

Roche was concerned about the statistical validity of the analysis, as any sub-group analyses needed to be accounted for statistically to avoid bias from multiple analyses. It was acknowledgement later in the press release that the analysis was exploratory, this should have been reflected in the headlines/bullet points to avoid misleading the audience. In inter-company dialogue, Merck Serono was unable to comment on Roche's statistical concerns and directed Roche to the study sponsor. This had not reassured Roche that Merck Serono could sufficiently substantiate the data and Roche alleged a breach of the Code.

The Panel considered that its general comments above in relation to the heading of the press release were relevant here. The sub-group analyses had not been placed in context of the study's failure to achieve its primary endpoint. In addition, it was not clear at the outset that the data was from a pre-planned exploratory analysis. The only reference to this was on the second page and there was no explanation that no confirmatory clinical conclusions could be drawn from such an analysis. In the Panel's view the press release invited the reader to draw such conclusions. Exploratory analyses should not be used as the basis for a robust comparison of medicines. The material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The Panel considered that the bullet point was misleading as alleged and ruled a breach of the Code. This ruling was upheld on appeal by Merck Serono.

The Panel noted Roche's allegation that Merck Serono was unable to substantiate the sub-group analysis. Merck Serono submitted that the bullet point in question was supported by the data presented at ESMO. However, the Panel noted that the ESMO presentation did not appear to cover statistical analysis of the sub-group although the abstract made it clear that the analysis was pre-planned. The Panel however did not have any accompanying transcript.

The Panel noted Roche's allegation that the sub-group analysis needed to be accounted for statistically to avoid bias from multiple analyses. On balance and on this very narrow point the Panel ruled that the bullet point in question was not capable of substantiation. A breach of the Code was ruled. This ruling was appealed by Merck Serono.

The Appeal Board noted that this was clearly a complex area. As the FIRE-3 study had progressed

it had started to become clear that patients with RAS wild-type mCRC responded better to therapy than those with RAS mutations. The analysis at issue in the press release involved only the RAS wild-type patients (n=342) and not the original ITT population (n=592). Although the Erbitux marketing authorisation had been restricted to patients with RAS wild-type mCRC, this was not the case when the press release was issued on 28 September 2013. In that regard the Appeal Board considered that only the data that was available on that date could be relied upon to substantiate the content of the press release.

The Appeal Board although concerned as to whether the analysis was sufficiently powered, considered that the bullet point was nonetheless factually correct and thus on balance, on this very narrow point, was capable of substantiation. No breach of the Code was ruled. The appeal on this point was successful.

Roche alleged that the second bullet point: 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)' seemed to suggest that there was no difference between the arms with respect to overall survival in the sub-group of patients with RAS mutant mCRC. In Europe, cetuximab was not licensed in RAS mutant mCRC and was actually contraindicated in the treatment of RAS mutant mCRC with certain chemotherapy combinations. No such restriction applied to bevacizumab. The licence restriction, or indeed any of the licence particulars (eg should only be used for EGFR-expressing tumours) for cetuximab were not mentioned in the press release.

The comparison was actually based on a pooled analysis of two different populations of patients with RAS mutations. There was no information in the press release that these findings were based on pooling data from two different time points, using two different testing methods. In 2008, patients with mutations in the KRAS EXON 2 gene were no longer included in the licences for anti-EGFRs in Europe. As a result of this, the FIRE-3 trial was amended in 2008 to exclude recruitment of patients with KRAS MT gene in EXON 2. The analysis based on patients with RAS MT mCRC recruited into the trial after the protocol amendment reported a median overall survival of 16.4 months in the cetuximab arm and 20.6 months in the bevacizumab arm. With the press release only utilising the pooled analysis data set it appeared that there was no difference in overall survival between the treatment arms without clarification that cetuximab was unlicensed (or even contraindicated) in patients with RAS MT disease.

Roche was extremely concerned that the claim implied cetuximab had efficacy in a population for which it was unlicensed or contraindicated as it compared itself with a medicine that was licensed for use in that population. The statement, whilst factually accurate, did not provide balance, was misleading in itself and with respect to the safety profile of cetuximab and did not encourage rationale use of the medicine.

The Panel considered that the comparison was misleading as it was not clear that it was based on a pooled analysis of two different populations of patients with RAS mutations from two different time points. The Panel ruled breaches of the Code as it considered that the context of the comparison was not clear and it was therefore misleading.

The Panel disagreed with Merck Serono's submission that the comparison made no efficacy claims for cetuximab. The Panel considered that the overall survival comparison of cetuximab with bevacizumab in patients with any RAS mutations was misleading as it implied that like bevacizumab, cetuximab was licensed for the treatment of RAS mutant mCRC which was not so. It was only licensed for EGFR expressing RAS wild-type metastatic colorectal cancer. In the Panel's view the failure of Merck Serono to place the bullet point within the context of cetuximab's licensed indication and the failure to mention relevant contraindications was misleading and did not encourage the rational use of cetuximab and breaches of the Code were ruled. A breach was also ruled as the comparison was misleading.

The Panel noted Merck Serono's submission that the press release had been widely distributed to medical journals and health journalists. The Panel noted its rulings above in relation to the misleading statements made about Erbitux and considered that in relation to the matters discussed above the press release, which had been made available to the public, was not factual and had not presented information about Erbitux, a prescription only medicine, in a balanced way and a breach was ruled.

Roche alleged that the quotation on page 2: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies…' was misleading as it did not contextualise the sub-group analysis. In addition, whilst it reflected the views of the investigator, the discussant at ESMO strongly questioned it and recommended that based on the available data it was not a paradigm shift and the forthcoming results of CALGB (a forthcoming study evaluating the efficacy of first-line cetuximab vs first-line bevacizumab with a primary endpoint of overall survival) should be awaited to provide more insights into the outcomes of FIRE-3. Using words as strong as 'paradigm shift' in a press release was exaggerated and could raise unfounded hopes and Roche alleged breaches of the Code.

Overall, given the number and nature of its concerns and the very real risk to patient safety, Roche alleged that the press release and promotional materials failed to maintain high standards. Roche also alleged that such a concerted campaign based on misleading and unbalanced claims of this nature put patient safety at risk and brought the industry into disrepute in breach of Clause 2.

The Panel noted its comments and rulings at above with regard to the data from the FIRE-3 study showing a 7.5 month increase in median overall survival when using Erbitux plus FOLFIRI as compared with using bevacizumab plus FOLFIRI in metastatic colorectal cancer. The Panel considered that the quotation 'Such a prolongation

is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies' was misleading as within the context of the median survival data it applied disproportionate weight to the results thereby exaggerating Erbitux's properties and consequently it did not encourage rational use. The Panel thus ruled breaches of the Code. The Panel noted its comments above regarding the provision of information to the public and similarly ruled a further breach of the Code. These rulings were upheld on appeal by Merck Serono.

The Panel considered that Merck Serono had failed to maintain high standards and ruled a breach in that regard.

The Panel noted that Clause 2 was used as a sign of particular censure and reserved for such use. The Panel noted that Roche had referred to patient safety. The Panel noted its rulings of breaches of the Code above. The Panel considered that it was very important that press releases about sensitive issues such as survival in cancer were fair, factual and not misleading. The press release had failed to reflect the study's primary endpoint and the product's licensed indications. In particular the headline claim about survival had been ruled in breach of the Code. The Panel considered that on balance the circumstances warranted such a ruling and a breach of the Clause 2 was ruled. This ruling was upheld on appeal by Merck Serono.

Roche Products Ltd complained about Merck Serono Limited's presentation showing the results of the FIRE-3 AIO (Arbeitgemeinschaft Internistische Onkologie) clinical trial in a UK press release (ref ERB13-0152) issued 28 September 2013 and also raised concerns about such data in unidentified Erbitux (cetuximab) promotional materials.

At that time Erbitux was indicated, *inter alia*, for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer (mCRC) in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX (folinic acid, fluorouracil and oxiplatin), and as a single agent in patients who had failed oxaliplatin and irinotecan-based therapy and who were intolerant to irinotecan.

Roche marketed Avastin (bevacizumab) which was indicated, *inter alia*, in combination with fluoropyrimidine-based chemotherapy for the treatment of adult patients with metastatic carcinoma of the colon or rectum.

In its response, Merck Serono stated that the press release was issued in the UK on 30 September 2013 and was sent to 40 medical and pharmaceutical titles, 23 health journalists at national print and online titles and 16 freelance health journalists.

COMPLAINT

Roche alleged that Merck Serono was in breach of Clauses 2, 7.2, 7.3, 7.4, 7.10, 9.1, 10.2, 12 and 22.2. Roche explained that the FIRE-3 clinical trial evaluated the superiority of cetuximab plus combination chemotherapy, compared with bevacizumab plus combination chemotherapy in the first-line treatment of KRAS wild-type metastatic colorectal cancer. The primary endpoint for the study was overall response rate. Secondary endpoints included progression-free survival and overall survival. Importantly it was not a treatment sequencing study as subsequent lines of treatment were not specified within the study protocol.

Roche stated that the primary analysis of the FIRE-3 study was presented at the American Society of Clinical Oncology (ASCO) 2013 and showed that the study failed to reach its primary endpoint. There was no significant difference in overall response rate (primary endpoint) between the two treatment arms. There was also no significant difference in progression-free survival between the two arms, but the authors reported increased overall survival in the arm receiving cetuximab plus chemotherapy as their first-line treatment (one of the secondary endpoints). The Kaplan-Meier curves of overall survival presented at ASCO 2013 showed that the lines, representing the different study arms, did not begin to separate until the 15-18 month time point. Given that the median time to first progression was approximately 10 months in both arms (10.0 and 10.3 months) and the reported median duration of first-line treatment was significantly shorter than this in both arms, there would appear to be significant grounds to question the degree to which the first-line treatment was responsible for any overall survival difference demonstrated.

Roche further stated that a second FIRE-3 analysis was presented in July 2013 at the World Congress on Gastrointestinal Cancer providing details of the second-line treatments administered to patients in the FIRE-3 trial. This analysis showed differences in the treatments received in the second-line setting by patients in the two arms. Furthermore, a large proportion of patients in FIRE-3 received treatment combinations in the second-line setting which were not current standard practice and were unavailable in the UK (as defined by the Cancer Drugs Fund listings) and were not prescribed newer options now available after first-line bevacizumab (eg aflibercept) – making FIRE-3 of questionable relevance to current UK clinical practice.

Roche stated that a further FIRE-3 analysis presented at the European Society for Medical Oncology (ESMO) European Cancer Congress (ECC), October 2013, showed the results of a pre-planned exploratory analysis of a sub-group of patients who were not only KRAS wild-type, but also NRAS wild-type (termed RAS wild-type). In that new sub-group of patients, the first-line cetuximab plus chemotherapy arm again failed to show a significant improvement over the bevacizumab plus chemotherapy arm in both overall response rate and progression free survival. However, the analysis showed a difference of 7.5 months in median overall survival between the two arms in favour of the group receiving cetuximab plus chemotherapy as their first-line regimen. As for the previous KRAS overall survival analysis, the Kaplan-Meier curves did not separate until well after completion of first-line treatments and first progression.

Roche became aware of a UK Merck Serono press release relating to the FIRE-3 trial analysis following the ESMO–ECC congress. The press release was headed: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'. Roche alleged that this press release was the source material for at least one media article 'Oncology Times', a journal with a readership of approximately 7,000 cancer professionals not restricted to oncologists. At the same time Roche was aware of similar messages being used in promotional materials in Ireland (with prescribing information stating it was for UK and Ireland) but was not sure if it was being used in the UK. Roche asked Merck Serono during inter-company dialogue on 4 December 2013 whether the statements were being used in promotional materials. Merck Serono did not confirm on this point until 3 February 2014.

Roche's specific concerns about the press release were as follows:

1 **Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study'**

Roche alleged that the overall survival statement in this heading was misleading because the FIRE-3 study failed to reach its primary endpoint of overall response rate. The heading was based on a sub-group analysis from this 'negative' phase III study. The fact that the study did not meet its primary endpoint was not prominently presented in the press release but was only mentioned midway down the second page of the press release. Roche alleged a breach of Clause 7.2 as the full nature of the study results were not represented in the heading or summary bullet points. There was well-established case precedent and Medicines and Healthcare Products Regulatory Agency (MHRA) Guidance that findings from secondary endpoints must be set within the context of the primary endpoint and that companies could not 'cherry pick' favourable findings. Merck Serono had now confirmed that it was using similar claims in its promotional materials. Given Merck Serono's uncompromising position that prominent qualification of such claims was not necessary, Roche strongly suspected that promotional materials currently in use would also not have the overall survival findings set in the context of the primary endpoint.

2 **First bullet point: 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 months to 33.1 months (p=0.011) …'**

Roche stated that this was the result of a sub-group analysis from the negative phase III study. Further contextualisation outlined in the background section was critical for the audience to be able to understand the clinical relevance of the data. The press release failed to set the finding clearly in the context of the overall study which failed to meet its primary endpoint. That key point was only briefly mentioned in paragraph 3, on the second page. In addition, the word 'exploratory' was only used much later in the press release to describe that analysis. Roche alleged that this rendered the press release misleading in breach of Clause 7.2.

Roche had stressed to Merck Serono that its concern with the analysis was not related to the number of patients included in the study but to the statistical validity of the analysis, as any sub-group analyses needed to be accounted for statistically to avoid bias from multiple analyses. It was acknowledged later in the press release that the analysis was exploratory therefore Roche would have anticipated that being reflected in the headlines/bullet points of the press release to avoid misleading the audience. Through inter-company dialogue, Merck Serono had submitted that it was unable to comment on Roche's statistical concerns and directed Roche to the study sponsor. This had not reassured Roche that Merck Serono was able to sufficiently substantiate the data it had used in its press release as it should have full awareness of the validity and relevance of data it used in a press release and promotional material. On the basis of that statement, received in the last round of inter-company dialogue, Roche alleged a breach of Clause 7.4.

Merck Serono eventually admitted, as Roche suspected, that similar claims were also being used in promotional materials and again, given its uncompromising stance in defence of the unqualified claim, Roche was extremely concerned at similar breaches in Merck Serono's promotional materials.

3 **Second bullet point: 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'**

Roche alleged that this bullet point seemed to serve no other purpose than to suggest that there was no difference between the arms with respect to overall survival in the sub-group of patients with RAS mutant mCRC. In Europe, cetuximab was not licensed in RAS mutant mCRC and was actually contraindicated in the treatment of RAS mutant mCRC with certain chemotherapy combinations. No such restriction applied to bevacizumab. The licence restriction, or indeed any of the licence particulars (eg should only be used for EGFR-expressing tumours) for cetuximab were not mentioned in the press release.

The comparison was actually based on a pooled analysis of two different populations of patients with RAS mutations (KRAS mutation pool EXON 2 according to Annals of Oncology, 2012, dated from 2006 to 2008 and advanced RAS mutation analysis of the FIRE-3 trial with mutations in EXON 3 and 4 of KRAS and EXON 2, 3, and 4 of the NRAS gene, which were included from October 2008). There was no information in the press release that these findings were based on pooling data from two different time points, using two different testing methods. In 2008, patients with mutations in the KRAS EXON 2 gene were no longer included in the

licences for anti-EGFRs in Europe. As a result of this, the FIRE-3 trial was amended in 2008 to exclude recruitment of patients with KRAS MT gene in EXON 2. The analysis based on patients with RAS MT mCRC recruited into the trial after the protocol amendment reported a median overall survival of 16.4 months in the cetuximab arm and 20.6 months in the bevacizumab arm. With the press release only utilising the pooled analysis data set it appeared that there was no difference in overall survival between the treatment arms without clarification that cetuximab was unlicensed (or even contraindicated) in patients with RAS MT disease. Although that may not be considered a breach of Clause 3.2 as a press release should be non-promotional it was certainly not in the spirit of the Code to make claims for a population outside the licence or contraindicated.

Roche was extremely concerned that the claim implied cetuximab had efficacy in a population for which it was unlicensed or contraindicated as it compared itself with a medicine that was licensed for use in that population. Merck Serono through inter-company dialogue did not share Roche's concerns with the statement and had indicated that it was included in the press release for balance. The statement, whilst factually accurate, did not provide balance and was misleading in itself and with respect to the safety profile of cetuximab. As such, it did not encourage rationale use of the medicine. Roche alleged a breach of Clauses 7.2, 7.3, and 7.10 and 22.2.

Whilst Merck Serono's latest letter dated 3 February 2014, assured Roche that that claim was not being used in promotional materials, Roche remained extremely concerned that Merck Serono failed to acknowledge the inappropriateness of including this bullet point in a press release, and the potentially serious consequences for patient safety.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies…'

Roche alleged that the quotation was misleading as it did not contextualise the sub-group analysis. In addition, whilst it reflected the views of the investigator, the discussant at ESMO strongly questioned it and recommended that based on the available data it was not a paradigm shift and the forthcoming results of the CALGB study (a forthcoming study evaluating the efficacy of first-line cetuximab vs first-line bevacizumab with a primary endpoint of overall survival) should be awaited to provide more insights into the outcomes of FIRE-3. Based on the nature of the analysis, a statement made in that way and using words as strong as 'paradigm shift' in a press release was exaggerated and could raise unfounded hopes. Roche alleged a breach of Clauses 7.2, 7.10, 10.2 and 22.2.

Based on its concerns, during inter-company dialogue, Roche requested that Merck Serono publish an erratum notice in relation to the article that appeared in the Oncology Times. Merck Serono declined this request as the companies had not resolved their concerns through inter-company dialogue. However, Roche was disappointed that Merck Serono did not consider it was responsible for press coverage that had been reproduced faithfully from its press release.

5 Overall

Given the number and nature of its concerns and the very real risk to patient safety, combined with Merck Serono's blunt refusal to relent on any of the points raised through inter-company dialogue, Roche alleged that the press release and promotional materials were in breach of Clause 9.1 as high standards had clearly not been maintained in the development of the items. Roche also alleged that such a concerted campaign based on misleading and unbalanced claims of this nature put patient safety at risk and in doing so, brought the industry into disrepute and was a breach of Clause 2.

RESPONSE

To give background and context to the complaint, Merck Serono submitted that the FIRE-3 study was conducted by the collaborative German AIO study group and was the first head to head comparison of cetuximab and bevacizumab in conjunction with a FOLFIRI chemotherapy backbone in the first-line treatment of KRAS wild-type (KRAS-wild-type) metastatic colorectal cancer. The primary endpoint was overall response rate (ORR) and the secondary endpoints included progression-free survival (PFS) and overall survival (OS). In addition to randomisation between the two arms the protocol included a recommendation with respect to second-line therapy. The appropriate page from the protocol was provided.

Merck Serono stated that FIRE-3 was initially presented at ASCO 2013 by the FIRE-3 study principal investigator and a copy of the abstract for the study was provided, the conclusion of which was that:

> 'ORR was comparable between arms in the ITT analysis, but favoured Arm A in assessable patients. Significantly superior OS was observed in KRAS-WT patients receiving cetuximab plus FOLFIRI as first-line treatment.'

The FIRE-3 principal investigator also stated in his presentation that:

> 'First-line treatment with FOLFIRI [folinic acid, fluorouracil and irinotecan] plus cetuximab resulted in a clinically meaningful difference in median OS of 3.7 months (HR 0.77) when compared to FOLFIRI plus bevacizumab.'

Merck Serono submitted that FIRE-3 was also considered of sufficient importance to be included in a press release by ASCO and a copy of the relevant sections was provided with independent comment on the study.

Merck Serono submitted that a further analysis of FIRE-3 was presented at the World Congress on Gastrointestinal Cancer (WGIC). Roche stated that 'there were differences in the treatments received in the second-line setting by patients in the two arms',

however data presented at the meeting showed that the chemotherapy backbone was very well balanced and similar numbers continued on the initial treatment strategy or switched to the alternate investigational agent. One of the conclusions was that:

> 'Frequencies of **antibody cross-over and continuation beyond progression** as well as chemotherapies were **balanced** in 2nd line treatment based on current evidence.'

Merck Serono noted that Roche had suggested that FIRE-3 was of 'questionable relevance to current UK practice'. However the use of cetuximab plus FOLFIRI followed by bevacizumab plus FOLFOX for the treatment of RAS wild-type metastatic colorectal cancer was subsequently endorsed by and added to the National Cancer Drugs Fund list and hence FIRE-3 was highly relevant to UK clinicians. Further evidence of the relevance to UK clinicians was the recently updated East Midlands Cancer Network guidelines for the treatment of metastatic colorectal cancer which included the cetuximab and FOLFIRI regimen used in FIRE-3 as a first-line treatment.

Merck Serono submitted that a pre-planned analysis of FIRE-3 investigating the effect of further mutations was presented at the ESMO-ECC congress. Merck Serono provided the presentation which showed that those patients who were both KRAS and NRAS wild-type - RAS wild-type - showed a difference of 7.5 months in OS in favour of the cetuximab arm over the bevacizumab arm.

An ESMO spokesperson commented on the study:

> 'The results show that the better RAS mutations can improve both the ORR and the OS in patients receiving cetuximab as compared to bevacizumab. This highlights the importance for detecting other RAS mutations to better select the group of patients who might benefit from anti-EGFR moAbs. These results might have an impact on daily clinical decisions as we are able to define a sub-group of patients most likely to benefit from FOLFIRI plus cetuximab in first-line setting.'

Similar prolongations in survival in the RAS wild-type population had been seen with another anti-EGFR agent, panitumumab, resulting in a change in the marketing authorisations of both agents to use in RAS wild-type patients only.

Merck Serono submitted than in summary, FIRE-3 had been shown to be of significant interest to ASCO, ESMO and the wider clinician community. The clinically significant increase in overall survival, particularly in the RAS wild-type group, led to debate regarding treatment strategy and the optimal use of biological agents in combination with chemotherapy. FIRE-3 was an ongoing study and questions around lack of difference in progression free survival remained to be answered. However, for Roche to describe FIRE-3 as a 'negative' study showed a wilful disregard for its important results.

Merck Serono's responded to Roche's specific concerns the press release as follows:

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study'

Merck Serono submitted that the heading was a factual description of the results of the new RAS wild-type analysis as presented at ESMO and was the only parameter that had significantly changed from the presentations at ASCO or WGIC. Furthermore the improvements in overall survival had been highlighted in the abstracts from both ASCO and ESMO so for Roche to allege that Merck Serono was 'cherry picking' data was a misrepresentation of the study results as presented by the investigators.

Merck Serono had always acknowledged that the primary endpoint of the study was not met and that was contained in the third paragraph of the press release immediately after the new results. The lack of difference in ORR and PFS had been reported in the ASCO press release and as there was no change in those endpoints it was not felt appropriate to include them in the headline.

Merck Serono confirmed that a similar claim regarding overall survival was being used in promotional material. That claim was always set in context and the wording 'The primary endpoint of ORR was not met in this study' was displayed on all materials where the claim was made.

Merck Serono submitted that the press release was factually correct, reflected the important results from a new analysis and acknowledged that the primary endpoint was not met. Accordingly the information was accurate, fair and reflected the evidence and was therefore not in breach of Clause 7.2.

2 First bullet point: 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 months to 33.1 months (p=0.011) …'

Merck Serono submitted that this was a large sub-group with 407 (69%) patients, the majority of the study population, evaluable for RAS status. The numbers evaluable for RAS status were balanced in both arms of the study and the statement was based on data presented at ESMO.

The summary of the presentation also included the statement:

> 'The RAS evaluable population was in all respects comparable to the ITT population.'

And concluded:

> 'Patients with all-RAS wild-type tumours have a clinically relevant survival benefit when first-line treatment with cetuximab is offered.'

Merck Serono submitted that the word 'exploratory' reflected that this was the first major study to evaluate RAS testing with Erbitux and reflected recent evidence that led the CHMP to recommend a change to the marketing authorisation for Erbitux from KRAS wild-type patients to all RAS wild-type metastatic colorectal cancer.

With regard to Roche's concerns regarding the statistical validity of the analysis, Merck Serono stated that these concerns had only been raised by Roche and had not been raised by either discussants at ASCO, WCGIC and ESMO or by any clinician to Merck Serono in the UK or elsewhere. Merck Serono disagreed that Roche's concerns that '…407 represents a large percentage of patients from the original ITT population but any sub-group analyses needs to be adjusted for statistically to avoid the issue of multiplicity arising from multiple analyses. Sub-groups may also be confounded as the benefits of the original randomisation are lost even if there are equal numbers of patients in the two groups' were valid in this case. The AIO study group which conducted the study, was a large and well respected group and was, in Merck Serono's view, competent to conduct an analysis of the data. Accordingly, Roche was advised that its concerns should be addressed to the AIO investigators directly who would be best placed to assist.

Merck Serono submitted that the bullet point again reflected the data as presented at ESMO, the importance of which was acknowledged by the ESMO spokesperson, and did not breach Clause 7.2. All claims were referenced to recently presented data, were capable of independent substantiation, and did not breach Clause 7.4.

3 Second bullet point: 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'

Merck Serono pointed out that information on the efficacy of Erbitux in both the KRAS wild-type and mutant populations and RAS wild-type and mutant populations were in Section 5.1 of the summary of product characteristics (SPC). This bullet point was included to provide full disclosure and reflected the data as presented at ESMO.

Merck Serono submitted that it took great care to ensure appropriate use of cetuximab though a variety of materials and services. Merck Serono had provided free KRAS testing to the NHS since the marketing authorisation was changed initially and now provided additional NRAS testing to ensure that clinicians could make a decision regarding what they considered to be appropriate for each patient by knowing the tumour biology, through the RAS biomarkers. Only with this knowledge could some treatments be included in or excluded from a patient's treatment plan. The availability of appropriate biomarker testing was deemed so essential to the appropriate use of anti-EGFR therapies such as cetuximab and panitumumab that the service would be taken over by NHS England from May 2014.

This press release was the only mention by Merck Serono of these data. Merck Serono was well aware that the marketing authorisation for cetuximab limited the use of cetuximab to only RAS wild-type patients and all promotional materials made this absolutely clear. [At the time of the press release Erbitux was indicated for KRAS wild-type patients]. Merck Serono submitted that Roche had wilfully misinterpreted this bullet point to manufacture a safety concern. Indeed, given its views on patient safety Merck Serono asked Roche in a letter of 3 February, whether these data had been included in Roche promotional materials to ensure accurate reflection of the evidence regarding bevacizumab in the RAS mutant population in compliance with Clause 7.2. To date no reply to this point had been received.

Merck Serono submitted that the bullet point was included to provide full disclosure of the study results in both the RAS wild-type and mutant population. No claims for efficacy were made and Merck Serono submitted that that the bullet point was not misleading, did not encourage inappropriate use of cetuximab or endanger patient safety. Accordingly Merck Serono refuted a breach of Clauses 7.2, 7.3, 7.10 or 22.2. Merck Serono submitted that as Clause 22.2 related to non-interventional studies it was not sure why Roche alleged a breach of that clause.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

Merck Serono submitted that the importance of the FIRE-3 results had also been reflected by the Cancer Drugs Fund recent inclusion of Erbitux and FOLFIRI as an allowed therapy for the treatment of first-line RAS wild-type metastatic colorectal cancer. The results of FIRE-3, an increase of 7.5 months survival, was one of the largest seen in any oncology study, the clinical significance of which had been widely recognised including by the European Medicines Agency (EMA) with the change in marketing authorisation.

5 Overall

This quotation was an accurate reflection of the investigator's views, did not encourage inappropriate use of cetuximab and was therefore not in breach of Clauses 7.2, 7.10, 10.2 or 22.2. As noted above, Clause 22.2 related to non-interventional studies.

In summary, Merck Serono submitted that the press release was an accurate reflection of the results of the FIRE-3 study presented at ESMO. The data were regarded as an important advance in the treatment of first-line RAS wild-type metastatic colorectal cancer. That the data were generally accepted was evidenced by the change in marketing authorisation and inclusion of the regimen in the National Cancer Drugs Fund list. The claims were not misleading, unbalanced nor did they put patient safety at risk as alleged and accordingly Merck Serono submitted that it had not breached Clauses 9.1 or 2.

* * * * *

In response to requests for further information, Merck Serono submitted that the change of the Erbitux licensed indication to all RAS wild-type metastatic colorectal cancer occurred in December 2013 and reflected the narrowing of the eligible licensed population from KRAS wild-type. Merck

Serono also provided a copy of the slides presented at the ASCO meeting, 2013 and highlighted a slide detailing the treatment duration. The median time of treatment in the FOLFIRI + cetuximab and FOLFIRI + bevacizumab arms was 4.8 months and 5.3 months respectively. Merck Serono submitted that the proportion of patients initially treated with FOLFIRI + cetuximab and which subsequently received bevacizumab as second-line treatment was similar to the proportion of patients which initially received FOLFIRI + bevacizumab and then received an anti-EGFR mAB such as cetuximab as second-line therapy. Merck Serono submitted that in both groups over 60% of patients received oxaliplatin as second-line treatment and thus the treatment arms were considered balanced. Merck Serono highlighted a slide from a presentation by Modest *et al* which gave further detail.

PANEL RULING

The Panel noted that the press release was dated 28 September 2013 and that Roche cited Clauses 7.2, 7.3, 7.4, 7.10, 10.2 , 22.2, 9.1 and 2 of the 2012 Second Edition (amended) Code. The 2014 Code came into operation on 1 January 2014 with a transition period until 30 April 2014 for newly introduced requirements. The clauses cited were not the same in the 2014 and Second 2012 Edition (amended) Codes, thus the Panel used the Second 2012 Edition (amended) Code.

The Panel noted that both parties had referred in general terms to UK promotional material. Roche, which as the complainant bore the burden of proof on the balance of probabilities, had not clearly identified any such material or made detailed allegations. The Panel decided to make its ruling upon the press release noting that any such rulings would apply to closely similar materials.

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study'

The Panel noted that the press release was dated 28 September 2013 and was headed 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 Months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'. Below, in slightly smaller text, were two bullet points; 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 to 33.1 months (p=0.011) in mCRC patients with RAS wild-type tumours receiving 1st line Erbitux plus FOLFIRI compared with patients receiving bevacizumab plus FOLFIRI' and 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'.

Text beneath referred to the phase III head-to-head trial which showed a 'clinically relevant improvement from Erbitux (cetuximab) plus FOLFIRI vs bevacizumab plus FOLFIRI as first-line treatment in metastatic colorectal cancer (mCRC) in patients with RAS wild-type tumours'.

The Panel noted that the FIRE-3 study was a multicentre randomised phase III trial investigating 5-FU, folinic acid and irinotecan (FOLFIRI) plus cetuximab versus FOLFIRI plus bevacizumab in first-line treatment of metastatic colorectal cancer (mCRC). The study failed to meet its primary endpoint of overall response rate (ORR). Secondary endpoints included median progression free survival (PFS) and median overall survival.

The FIRE-3 study principal investigator gave the FIRE-3 oral presentation at the European Cancer Congress, the summary of his presentation stated 'OS was markedly superior (Δ = 7.5 months, HR 0.70) in all RAS wild-type patients receiving first-line therapy with cetuximab (p=0.011)'. The presentation concluded that upfront determination of RAS (KRAS and NRAS) mutation status appeared to be highly recommendable in patients with metastatic disease and concluded that 'Patients with all-RAS wild-type tumours have a clinically relevant survival benefit when first-line treatment with cetuximab is offered'.

The Panel noted that in its general comments Roche queried the degree to which the first-line treatment was responsible for any overall survival difference demonstrated as the Kaplan-Meier curves of overall survival representing the different study arms presented at ASCO 2013 did not begin to separate until the 15-18 month time point whereas the median time to first progression was approximately 10 months in both arms (10.0 and 10.3 months) and the reported median duration of first-line treatment was significantly shorter than this in both arms. The Panel noted that Merck Serono did not provide much detail in response to Roche's statement other than highlighting the median duration of treatment in the FOLFIRI + cetuximab and FOLFIRI + bevacizumab arms which was 4.8 months and 5.3 months respectively. The Panel further noted that only 15.2% of patients in the FOLFIRI + cetuximab treatment arm and 11.4% in the FOLFIRI + bevacizumab treatment arm had received Anti-EGFR mAB treatment such as cetuximab as part of their second-line treatment. The Panel did not consider this point further as there was no specific allegation.

The Panel noted Roche's allegation that the overall survival statement in the press release heading was misleading because the fact that the FIRE-3 study failed to reach its primary endpoint was not prominently presented within the press release and the full nature of the study results were not represented in the heading or summary bullet points. The Panel disagreed with Merck Serono's decision that as the lack of difference in ORR and PFS had previously been reported in the ASCO press release and as there was no change in these endpoints it was not considered appropriate to include them in the heading. It was a well established principal of the Code that each claim had to be capable of standing alone. The Panel considered that the heading, 'Merck Serono's Erbitux Significantly Extends Survival to 7.5 Months in mCRC Wild-Type Patients When Compared with Bevacizumab:

New Analysis of FIRE-3 AIO Study', was not a fair reflection of the overall data; it had not been placed within context of the study's primary outcome. The reference to the study's failure to meet its primary endpoint of objective response rate based on investigators' read in patients with KRAS EXON 2 wild-type tumours appeared in the third paragraph on page 2 and was insufficient to counter the heading. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the secondary endpoint findings. The heading was therefore misleading as alleged and the Panel ruled a breach of Clauses 7.2. This ruling was appealed.

2 First bullet point in press release: 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival from 25.6 months to 33.1 months (p=0.011) …'

The Panel noted Roche's allegation that the first bullet point 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival (OS) from 25.6 to 33.1 months (p=0.011) in mCRC patients with RAS wild-type tumours receiving 1st line Erbitux plus FOLFIRI compared with patients receiving bevacizumab plus FOLFIRI' similarly failed to set this finding clearly in the context of the overall study. The Panel considered that its general comments above in relation to the heading (point 1 above) were relevant here. The sub-group analyses had not been placed in context of the study's failure to achieve its primary endpoint. In addition, the Panel was concerned that the press release did not make it clear at the outset that the data was from a pre-planned exploratory analysis. The only reference to this was on the second page of the press release and there was no explanation that no confirmatory clinical conclusions could be drawn from such an analysis. In the opinion of the Panel the press release invited the reader to draw such conclusions. Exploratory analyses should not be used as the basis for a robust comparison of medicines. The material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The Panel considered that the bullet point was misleading as alleged and ruled a breach of Clause 7.2. This ruling was appealed.

The Panel noted Roche's submission that during inter-company dialogue Merck Serono was unable to comment on its statistical concerns about the analyses and directed it to the study sponsor. Roche alleged that Merck Serono was therefore unable to substantiate the sub-group analysis and was thus in breach of Clause 7.4. The Panel noted Merck Serono's submission that it disagreed that Roche's concerns were valid and directed it to the AIO investigators who would be best placed to assist with its query. The Panel noted that Roche had not alleged a breach of Clause 7.5 which required substantiation for any information, claim and comparison to be provided as soon as possible and certainly within 10 working days. The Panel was concerned that Merck Serono did not comment on the statistical validity of the sub-group analysis or contact the study organisers and provide feedback to Roche during inter-company dialogue. Nonetheless Roche had alleged a breach of Clause 7.4 which required that information, claims and comparisons be capable of substantiation. Merck Serono submitted that the bullet point in question was supported by the data presented at ESMO. However, the Panel noted that the ESMO presentation did not appear to cover statistical analysis of the sub-group although the abstract made it clear that the analysis was pre-planned. The Panel however did not have any accompanying transcript.

The Panel noted Roche's allegation that the sub-group analysis needed to be accounted for statistically to avoid bias from multiple analyses. On balance, and on this very narrow point, the Panel ruled that the bullet point in question was not capable of substantiation. A breach of Clause 7.4 was ruled. This ruling was appealed.

3 Second bullet point: 'In the group with any RAS mutations, patients who received Erbitux in 1st line reached a median OS of 20.3 months vs. 20.6 months in the group that was treated with bevacizumab in 1st line (p=0.60)'

The Panel noted Roche's allegation that the second bullet point 'In the group with any RAS mutations, patients who received Erbitux in first-line reached a median OS of 20.3 months vs 20.6 months in the group that was treated with bevacizumab in 1st Line (p=0.60)' suggested that there was no difference between the arms with respect to overall survival in the sub-group of patients with RAS mutant mCRC. The Panel noted Roche's submission that cetuximab was not licensed for RAS mutant mCRC in Europe and was contraindicated in the treatment of RAS mutant mCRC with certain chemotherapy combinations. Roche was concerned that neither this licence restriction nor the licensed indication of cetuximab were mentioned in the press release which was alleged to be misleading and not to encourage the rational use of cetuximab.

The Panel considered that the comparison was misleading as it was not clear that it was based on a pooled analysis of two different populations of patients with RAS mutations from two different time points. The Panel ruled a breach of Clauses 7.2 and 7.3 as it considered that the context of the comparison was not clear and it was therefore misleading. This ruling was accepted.

The Panel disagreed with Merck Serono's submission that the comparison made no efficacy claims for cetuximab. The Panel considered that the overall survival comparison of cetuximab with bevacizumab in patients with any RAS mutations was misleading as it implied that like bevacizumab, cetuximab was licensed for the treatment of RAS mutant mCRC which was not so. It was only licensed for EGFR expressing RAS wild-type metastatic colorectal cancer. [At the time of the press release Erbitux was only licensed for EGFR expressing KRAS wild-type metastatic colorectal cancer]. In the Panel's view, the failure of Merck Serono to place the bullet point within the context of cetuximab's licensed indication and the failure to mention relevant contraindications was misleading and did not encourage the rational use of cetuximab and breaches of Clause 7.2 and 7.10

were ruled. A breach of Clause 7.3 was also ruled as the comparison was misleading. These rulings were accepted. The Panel noted that Roche made reference to Clause 3.2 but no allegation was made and thus the Panel made no ruling in this regard.

The Panel noted that Merck Serono was unsure why Roche had raised Clause 22.2 as it related to non-interventional studies. This was so in the 2014 Code. However, both the allegation and response appeared to relate to Clause 22.2 of the 2012 Second Edition (amended) Code which required, *inter alia*, that information about prescription only medicines which was made available to the public either directly or indirectly, must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. The Panel noted Merck Serono's submission that the press release had been sent to forty medical and pharmaceutical titles, twenty-three health journalists at national print and online titles and sixteen freelance health journalists. The Panel noted its rulings above in relation to the misleading statements made about Erbitux and considered that in relation to the matters discussed above the press release was not factual and had not presented information about Erbitux in a balanced way contrary to Clause 22.2. A breach of Clause 22.2 was ruled. This ruling was accepted.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

The Panel noted Roche's concern regarding the statement 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies' which was referenced to the FIRE-3 principal investigator, and was made in reference the new median survival data. The supplementary information to Clause 10.2 stated that any quotation used in promotional material must comply with the Code.

The Panel noted its comments and rulings at points 1 and 2 above with regard to the data from the FIRE-3 study showing a 7.5 month increase in median overall survival when using Erbitux plus FOLFIRI as compared with using bevacizumab plus FOLFIRI in metastatic colorectal cancer. The Panel considered that the quotation was misleading as within the context of the median survival data it applied disproportionate weight to the results thereby exaggerating Erbitux's properties and consequently it did not encourage the product's rational use. The Panel thus ruled breaches of Clauses 7.2, 7.10 and 10.2. The Panel noted its comments above with regard to Clause 22.2 and similarly ruled a breach of that clause. These rulings were appealed.

5 Overall

The Panel noted all of its rulings of breaches of the Code above and considered that Merck Serono had failed to maintain high standards. A breach of Clause 9.1 was ruled. This ruling was appealed.

With regard to Clause 2, the Panel noted that it was used as a sign of particular censure and reserved for such use. The supplementary information to Clause 2 gave examples including prejudicing patient safety. The Panel noted that Roche had referred to patient safety. The Panel noted its rulings of breaches of the Code above. The Panel considered that it was very important that press releases about sensitive issues such as survival in cancer were fair, factual and not misleading. The press release had failed to reflect the study's primary endpoint and the product's licensed indications. In particular the headline claim about survival had been ruled in breach of the Code. The Panel considered that on balance the circumstances warranted such a ruling and a breach of Clause 2 was ruled. This ruling was appealed.

APPEAL BY MERCK SERONO

Prior to laying out the points of appeal, Merck Serono noted that setting the context within which the press statement was released (in terms of the licence for Erbitux (cetuximab) and the evolving scientific knowledge regarding RAS mutations and their relation to efficacy) would be helpful to the Appeal Board.

Merck Serono noted that one of the principal complaints by Roche of the press release at issue related to the secondary endpoint of median overall survival (OS) and comparison of that endpoint in a subset of patients in the cetuximab treatment arm and patients in the bevacizumab treatment arm; the outcome of 33.1 vs 25.6 months (p=0.011) favoured cetuximab.

Merck Serono noted that the primary endpoint of the study was the overall objective response rate (ORR) which did not show any statistically significant difference between treatment arms. Due to the non-significance of the primary endpoint Roche alleged that the comparison was in effect misleading; the Panel agreed. Whilst this complaint had been going through the complaint's procedure, this comparison (and other associated data) had also been reviewed by the EMA, and following a positive opinion on 26 June 2014 these data were now incorporated into the cetuximab SPC.

Merck Serono submitted that the information promulgated in the press statement was therefore capable of withstanding detailed scrutiny. Given that these data were now being incorporated into the licence for cetuximab, it was accurate and did not mislead, and this was the basis for the appeal.

Current Licence

'For the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer

- In combination with irinotecan-based chemotherapy
- In first-line in combination with FOLFOX
- As a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.'

Merck Serono submitted that FOLFOX and FOLFIRI were two principal chemotherapy regimens used in

the treatment of metastatic colorectal cancer (mCRC) upon which biological agents such as cetuximab or bevacizumab might be added with a view to improving outcomes compared with chemotherapy alone. Both these chemotherapy regimens were acceptable within the licence for use with cetuximab. As the chemotherapy background had not changed within the licence, for clarity, discussion of changes to the licensed indication for cetuximab would be limited to discussion of the RAS tumour (mCRC) status, since this was the key element of change within the licence, and also key in understanding the appeal.

Merck Serono submitted that when cetuximab was first licensed in 2004 it was indicated for the treatment of EGFR-expressing mCRC. Subsequently the licence had been specifically amended to inform further the patients who were appropriate for treatment with cetuximab, and importantly identifying those patients (based upon analysis of tumour biomarkers) who were highly unlikely to respond to treatment, and as such should not have treatment with cetuximab initiated.

KRAS licence update

Merck Serono submitted that the first change to the licence in this respect occurred in 2008 when it became increasingly clear that the activity of EGFR targeting therapies was restricted to patients who did not express activating mutations of KRAS proteins (see below for details), hence only patients with proven KRAS wild-type, [ie non mutant] tumour status should be considered for treatment with cetuximab. This licence indication remained unchanged until December 2013, and hence when the press statement was released (28 September 2013) was the licensed indication for cetuximab (SPC dated September 2008).

RAS licence update

Merck Serono submitted that a second change to the licence occurred in December 2013 with the reporting of new studies, in particular OPUS, and followed identification of other mutations beyond those originally examined (KRAS EXON 2) to include mutations in EXONS 3, and 4 of genes expressing KRAS activity, and also in EXONS 2, 3 and 4 of genes expressing NRAS activity. Analysis had indicated that in patients with mCRC expressing mutations of either (or both) KRAS and NRAS (EXONS 2, 3 and 4) were again highly unlikely to respond to treatment with EGFR targeted therapies.

Merck Serono submitted that after December 2013, the licence for cetuximab was therefore restricted to patients with EGFR-expressing, RAS wild-type metastatic colorectal cancer, ie, no mutations within the loci described immediately above. It was the outcomes of this patient sub-group from within the FIRE-3 study that was reported upon within the press release at issue, and in particular it was stated that the median OS in mCRC RAS wild-type patients receiving first-line FOLFIRI plus cetuximab (FOLFIRI/cetuximab) was 33.1 months compared with 25.6 months in patients receiving first-line FOLFIRI plus bevacizumab (FOLFIRI/bevacizumab). This RAS wild-type patient population was (and still was) within licence since KRAS wild-type (as stipulated within the licence at that time) was a broader patient population; ie RAS wild-type was a subset within the KRAS wild-type population (SPC dated December 2013).

Merck Serono submitted that the results of the FIRE-3 study and analyses of the subset of patients with RAS wild-type status has been reviewed by the EMA, following which a positive opinion from the CHMP on 26 June 2014 was concluded and the licence for cetuximab was being updated to include these efficacy data (Updated SPC; CHMP positive opinion dated 26 June 2014).

Mechanism of action of EGFR targeted therapies

Merck Serono submitted that cetuximab was a chimeric monoclonal immunoglobulin G1 (IgG1) antibody directed at the epidermal growth factor receptor (EGFR). EGFR signalling pathways were involved in, amongst other activities, the control of cell survival, cell cycle progression, cell migration and invasion/metastasis. Cetuximab bound to the EGFR with a higher affinity than endogenous ligands, thus effectively blocking the receptor and subsequent intra-cellular signalling, and leading also to internalisation of the EGFR. Cetuximab also targeted cytotoxic immune effector cells towards EGFR-expressing tumour cells; an example of antibody dependent cell-mediated cytotoxicity (ADCC). Cetuximab therefore led to inhibition of intra-cellular signalling associated with EGFR activation and hence interfered with cell function, an action which ultimately could be lethal to that cell, as well as initiating ADCC.

KRAS and RAS proteins

Merck Serono submitted that RAS proteins were a ubiquitous group of intra-cellular proteins implicated in a number of down-stream signalling processes which normally controlled cell cycling; as such they were also known as proto-oncogenes. Under normal circumstances these proteins could be 'activated' following stimulation of EGF-receptors; their subsequent and controlled 'deactivation' allowed for regulated activity.

Merck Serono submitted that RAS proteins might also be 'activated' via mutations of the RAS genes leading to unregulated activity which bypassed the normal EGF-receptor activation (and subsequent deactivation) sequence. Since activation of RAS proteins via these gene mutations were independent of the EGFR signalling pathway it followed that a therapy targeting an EGF- receptor, such as cetuximab, would be highly unlikely to be effective against a tumour cell with mutated RAS onco-genes. For clarity in the document, the RAS protein family could be divided broadly into two principal groups, NRAS, KRAS, (and a third group HRAS not discussed further here), which were collectively known as RAS proteins. The nomenclature for the protein groups was based upon the *in vitro* models from which they were first identified;

RAS **Ra**t **s**arcoma proto-oncogene
KRAS **K**irsten **ra**t **s**arcoma 2 viral oncogene homolog
NRAS **N**eurobalstoma **RAS** viral oncogene homolog
HRAS v-Ha-**RAS** Harvey rat.

Merck Serono submitted that since cetuximab was first licensed (and another EGFR targeting therapy, panitumumab also gained its licence) there had been a growing awareness of the patient population for whom, because of identifiable tumour RAS status, EGFR targeting therapies might be an appropriate treatment, and also those patients in whom such treatment should not be initiated because of the likelihood that the treatment would not be effective ie those patients whose tumours would be predicted as highly likely to be resistant to cetuximab.

Merck Serono submitted that scientific knowledge had evolved over the past few years, along with RAS testing, that now enabled these distinct patients populations (those with RAS mutations, and those without mutations ie RAS wild-type) to be identified with some certainty such that patients did not receive an EGFR targeted therapy inappropriately. This was not the case at the start of many of the clinical trials involving EGFR targeted therapies, some of which had only recently reported results (eg FIRE-3), and indeed others which had only reported interim results (eg CALGB 80405). Such trials had included initially patients in whom mCRC KRAS status was unknown; subsequently, with the awareness of the importance of KRAS testing the entry criteria for these studies was amended to exclude patients with known KRAS mutations.

Investigators therefore had become aware (retrospectively) that some of the patients in the cetuximab treatment arm would have had tumours which based upon KRAS testing would have been resistant to that treatment and hence those patients would not have been likely to derive any additional benefit over the use of chemotherapy alone. Conversely there would also be patients for whom an EGFR targeted therapy was an appropriate option as an add on to chemotherapy and it would be important to report such patients separately from those predicted to be resistant in order to define firstly the appropriate patient population for EGFR targeted therapy, and secondly to determine the potential benefit of such treatment. Furthermore, additional mutations of KRAS and NRAS had been identified that also predicted likely resistance to cetuximab treatment, again increasing the necessity to correctly identify patients prior to initiation of cetuximab treatment, and also to report the outcomes by different RAS mutation status rather than by broad populations.

Evolution of RAS testing

Merck Serono submitted that initial RAS testing sought to identify mutations of the KRAS group at genetic 'hotspots'. The most frequently involved was at EXON 2, (codons 12 and 13) and accounted for most of the known genetic mutations of the RAS system. Patients with KRAS mutations at these sites were then excluded from study entry via protocol amendments. Such amendments occurred in several studies including FIRE-3.

Additional mutations were subsequently identified (at a much lower frequency) at KRAS EXONS 3 and 4, and also at NRAS EXONS 2, 3 and 4 which also predicted the likelihood of resistance to cetuximab. Consequently, in reporting the results of such studies, (via analyses of the primary endpoint in the intention-to-treat (ITT) population which would contain a subset of patients with RAS mutations making them resistant to cetuximab therapy) care should therefore be exercised in drawing absolute clinical conclusions from such analyses, even though the statistical methodology was correct.

Post-hoc analysis of patient subsets from studies such as OPUS and CRYSTAL had enabled a more informed understanding of the potential benefit (or otherwise) of using an EGFR targeted therapy, based upon analysis of RAS mutations.

The Phase II OPUS study which investigated first-line use of cetuximab plus FOLFOX4 vs FOLFOX4 alone had indicated that for the KRAS wild-type population (within licence until December 2013) the median OS was 22.8 months vs 18.5 months in favour of cetuximab compared with chemotherapy alone (HR 0.855; 95% CI 0.599, 1.219 p=0.3854 not significant). For the KRAS mutant population median OS was 13.4 months vs 17.5 months in favour of FOLFOX4 alone (HR 1.29; 95% CI 0.873, 1.902 p=0.2) ie a negative effect of cetuximab when combined with FOLFOX4 in this defined (KRAS mutant) patient population who were highly likely to be resistant to EGFR targeting therapies.

Although patient numbers were small (FOLFOX4/ cetuximab KRAS wild-type n=82: FOLFOX4/ cetuximab KRAS mutant n=77) and p values did not achieve statistical significance, the directional outcomes of these exploratory analysis supported a licence change for cetuximab in 2008 which restricted use to patients with KRAS wild-type status (SPC September 2008).

Merck Serono submitted that exploratory analyses of other subsets of patients within OPUS had further supported this restriction; in patients with any RAS mutation and who received FOLFOX4/ cetuximab median OS was 13.5 months compared with 17.8 months with FOLFOX4 alone; ie a negative effect for patients with RAS mutations receiving cetuximab plus FOLFOX4 (P=0.157). Although not significant statistically, the tumour cell biology and mechanism of action for EGFR targeted therapies provided compelling reasons for not treating patients with RAS mutations with cetuximab (SPC December 2013).

Merck Serono submitted that the converse is also true, ie exploratory analyses of subsets of patients from these studies had also helped identify patients for which treatment outcomes were improved. In the CRYSTAL study which compared cetuximab with FOLFIRI to FOLFIRI alone, a positive outcome was noted in the analysis of patients with KRAS wild-type status receiving cetuximab as an add-on compared with FOLFIRI alone; 23.5 vs 20.0 months HR 0.8;

95% CI 0.67, 0.95 p=0.0093. No such benefit was seen in the KRAS mutation population. Importantly within the KRAS wild-type population receiving FOLFIRI/cetuximab the PFS and ORR were also improved compared with those patients receiving FOLFIRI alone, both achieving statistical significance p=0.0012 and <0.0001 respectively (see SPC June 2009).

Merck Serono submitted that the KRAS wild-type population in CYRSTAL also included some patients with other RAS mutations and who were consequently resistant to cetuximab treatment. Further analysis of additional RAS mutations (beyond KRAS EXON 2) indicated that in the RAS wild-type population, those patients who had received cetuximab plus FOLFIRI had a median OS of 28.4 vs 20.2 months compared with FOLFIRI alone, HR 0.69; 95% CI 0.54, 0.88 p=0.0024. For those patients with any RAS mutation there was no statistical difference between treatment arms: median OS 16.4 vs 17.7 HR 1.05 95% CI 0.86, 1.28 p=0.64. Again supporting this improvement in overall survival for the RAS wild-type subset of patients, the data for PFS an ORR also achieved statistical significance p=0.0024 and <0.0001 respectively (updated SPC June 2014).

Merck Serono submitted that although exploratory, the analyses of patient subsets based on RAS status (mutation or wild-type) nevertheless allowed a rationale review of outcomes based upon biomarkers which could be used for appropriate patient selection for treatment (or otherwise) with EGFR targeted therapies. It was also obvious that exclusion of patients (for whom resistance to therapy was highly likely) would improve the outcome of an analysis for EGFR targeted therapies. Under these circumstances, and in particular as the licence for cetuximab had been amended to exclude patients with RAS mutations from treatment, these types of analyses [x patient subsets] of results from older clinical trials that were now being reported would continue, and also would yield important information about treatment outcomes.

Merck Serono submitted that dismissing such exploratory analyses on the basis of purely statistical grounds would not be appropriate clinically, and could affect patient care. In purely statistical terms the construct hypothesis had changed such that the comparison from the ITT population were not strictly of clinical relevance today since the ITT population included patients with resistance to EGFR targeted therapies. Of relevance was the comparison of one treatment used for appropriate patients against another also being used for appropriate patients. It was within this context that the comparison of cetuximab with bevazicumab was made in the press statement.

Analysis of FIRE-3 and update to the licence for cetuximab

Merck Serono submitted that FIRE-3 was an open label, randomised (1:1), phase III study which investigated the efficacy of FOLFIRI in combination with cetuximab vs bevacizumab in first-line treatment of mCRC. The study was initiated in 2007 and a 'cut-off' date was April 2013. Initially unselected mCRC patients were enrolled, and following an amendment in October 2008, KRAS EXON 2 wild-type patients only were included; this latter group forming the ITT population (n=592). Other amendments to the study were considered minor. The study was conducted in Germany and Austria in 150 active sites.

Second-line therapy recommended after FOLFIRI + cetuximab was FOLFOX (plus bevacizumab 'if needed') and after FOLFIRI + bevacizumab: irinotecan + cetuximab. The primary endpoint of the ITT analysis was ORR using investigator evaluation (RECIST 1.0); these occurred after 6 and 12 weeks, and thereafter every 10 weeks. Secondary endpoints included PFS and median OS. Where tumour samples were available, the mutation status of KRAS EXON 2 (codons 12 and 13), EXON 3 (codon 61) and EXON 4 (codon 146), and NRAS EXON 2 (codons 12 and 13), EXON 3 (codons 59 and 61), and EXON 4 (codons 117 and 146) were analysed. In total 753 patients were enrolled, of which 113 patients were subsequently identified with KRAS EXON 2 mutations. From the ITT population of 592 KRAS EXON 2 wild-type patients, 407 (69%) had had tissue samples of the tumour collected and suitable for expanded RAS analysis (the RAS evaluable population). Of this RAS evaluable population 342 (FOLFIRI/cetuximab n=171, FOLFIRI/bevacizumab n=171) were RAS wild-type and 65 had 'new' RAS mutations. The 'new' RAS mutations plus the 113 KRAS EXON 2 mutations collectively formed the RAS mutation population (n=178; 92 with FOLFIRI/cetuximab and 86 with FOLFIRI/bevacizumab). Results for the ITT KRAS EXON 2 wild-type, RAS wild-type and RAS mutation populations were presented below (updated SPC June 2014);

KRAS wild-type ITT population (n=592)

ORR (primary endpoint) cetuximab + FOLFIRI 62%, bevacizumab + FOLFIRI 58%; p=0.183: Primary endpoint not met

PFS (secondary endpoint) cetuximab + FOLFIRI 10 months, bevacizumab + FOLFIRI 10.3 months: p=0.547

Median OS (secondary endpoint) cetuximab + FOLFIRI 28.7 months, bev + FOLFIRI 25 months

HR=0.77 p=0.017, Δ=3.7 months in favour of cetuximab arm

RAS wild-type population (n=342)

OORR: FOLFIRI/cetuximab 65.5%, FOLFIRI/bevacizumab 59.6% p=0.32 not significant

PFS: FOLFIRI/cetuximab 10.4 months, FOLFIRI/bevacizumab 10.2 months p=0.54 not significant

Median OS: FOLFIRI/cetuximab 33.1 months, FOLFIRI/bevacizumab 25.6 months p=0.011

HR 0.7 (95%CI 0.53 – 0.92) Δ=7.5 months in favour of cetuximab arm

RAS mutation population (n=178)

(RAS mutations =KRAS EXON 2 mutations (n=113) plus 'new' RAS mutations (n=65)

OORR: FOLFIRI/cetuximab 38.o%, FOLFIRI/ bevacizumab 51.2% P=0.097 (favours bevacizumab)

PFS: FOLFIRI/cetuximab 7.5 months, FOLFIRI/ bevacizumab 10.1 months p=0.085

HR 1.31 Δ=2.6 months in favour of bevacizumab arm

Median OS; FOLFIRI/cetuximab 20.3 months, FOLFIRI/bevacizumab 20.6 months p=0.6

Difference not significant

Discussion of results of FIRE-3.

Merck Serono submitted that though the primary endpoint of the ITT population was not significant in terms of ORR, pre-planned exploratory analysis of previously identified patient sub-types was performed. The cetuximab arm of this ITT population with KRAS EXON 2 wild-type status confirmed would still include a portion of patients who had mutations at loci other than KRAS EXON 2 (65 such patients were identified). Exclusion of these patients from analysis was appropriate since they were predicted to be resistant to treatment on the basis of tumour biology and the mechanism of action of cetuximab. Analysis of the RAS wild-type population would therefore yield a more precise view of the benefit of cetuximab when added to FOLFIRI in an appropriately defined population. This was a sensible course of action to pursue in order to help inform clinical practice.

Merck Serono submitted that the results for the overall ITT population indicated a small but statistically significant difference of 3.7 months in terms of median OS for the cetuximab arm compared with the bevacizumab arm. This population contained patients resistant to cetuximab (KRAS and NRAS mutations), hence removing them and then reanalysing the remaining patients (RAS wild-type) would increase this survival difference, ie to a Δ of 7.5 months in favour of cetuximab.

Merck Serono submitted that this was not a chance finding, but followed analysis of the data based upon testing for RAS mutations, and was reflective of tumour biology and removal of patients likely to be resistant to EGFR therapy. This was logical to do as it informs selection of appropriate therapy for individual patients.

Merck Serono submitted that it would now be wrong to initiate treatment with cetuximab in patients without knowledge of their RAS status as clinical studies had shown unequivocally that patients with RAS mutational status did not respond to cetuximab (and the licence had been updated to reflect this). Under such circumstances patients would have a negative effect from receiving cetuximab in terms of gaining no efficacy benefit, but experiencing side effects of treatment. This was not however known when FIRE-3, and other studies in mCRC were initiated, and as this new information about potential response/resistance had become available it was important to report data for patients within these studies by RAS status so that patients in whom cetuximab had been appropriately administered could be identified and the outcomes scrutinised.

Merck Serono submitted that there were however several key questions with regard to the validity of the survival data for RAS wild-type patients in the FIRE-3 study; Why if there was a survival advantage for cetuximab, was there no difference between treatment arms for PFS? Why did the Kalpan-Meier curves only start to separate long after cessation of first-line treatment? Responses addressing these important questions were submitted to the EMA when updating the licence for cetuximab in respect of the CRYSTAL and FIRE-3 efficacy data.

Merck Serono submitted that it could be considered surprising that a survival advantage was seen in FIRE-3 for patients with RAS wild-type status when there was no real difference in PFS between the treatment arms. In patients with RAS mutant and wild-type status, post progression survival seems to be longer in the cetuximab treated arm. In the case of RAS mutations, due to the fact that these tumours were highly likely to be resistant to EGFR targeted therapies, improved post progression survival could not be due to post progression effects of cetuximab first-line.

Merck Serono submitted that this was similar to findings noted in the PEAK study which investigated panitumumb (another EGFR targeted therapy) or bevacizumb as add on to FOLFOX6; both median OS and survival post-progression were superior in the EGFR targeted treatment arm when compared with bevacizumab. This might be related either to some other actions of EGFR targeted therapies, or possibly due to some inherent property of bevacizumab (Schwatzberg *et al* 2014).

Merck Serono submitted that recently the results of study ML18147 (2013) which investigated prolonged treatment with bevacizumab as add-on to next-line chemotherapy compared with next-line chemotherapy alone in patients failing first-line chemotherapy + bevacizumab in mCRC. Patients with progressive disease on first-line therapy within 3 months, or bevacizumab administered for less than 3 months were excluded from the study. The results reported improvement in overall survival for the prolonged treatment group, HR 0.8 (p=0.006) (Bennouna *et al* 2013).

Merck Serono submitted that as no likely differences in second-line treatment were reported from the FIRE-3 study the prolonged post-progression survival in the cetuximab arm might be related to stopping bevacizumab at time of progression. Theoretically, cessation of bevacizumab might lead to tumour neoangiogenesis and hence an enhanced tumour progression rate in some patients receiving bevacizumab. Such a theory would fit reasonably well with the ML18147 study, and might also help to explain the positive outcome of prolonged

bevacizumab treatment in that study. Such a theory might also help explain the late separation of the Kaplan-Meier curve in respect of overall survival in the FIRE-3 study whereby neoangiogenesis following cessation of treatment in the bevacizumab arm led to a faster rate of tumour progression, the outcome of which was expressed ultimately within the survival curves.

Merck Serono submitted that in addressing the issue of no significant differences between the primary analysis of ORR in the ITT population n=592, which was 62% for FOLFIRI/cetuximab and 58% FOLFIRI/bevacizumab, (difference not significant), further analysis had also been performed. The ITT population consisted of patients with KRAS wild-type status, and that population included some patients also with RAS wild-type mutations which would impart resistance to cetuximab therapy. These patients should therefore be excluded for mechanistic reasons as explained previously. The ORR was also measured by investigators within the open label FIRE-3 study using Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 (a set of rules to define when cancer patients improved ('respond'), stayed the same ('stable') or worsened ('progression') during treatment). ORR consisted of those patients with a complete plus partial response to therapy. An independent evaluation of tumour response had also been performed, and by reviewers blinded to treatment and patient data using RECIST 1.1. Results of this independent evaluation of ORR had recently been reported (Heinemann *et al* 2014), and might help explain the survival advantage accrued to the cetuximab treatment arm in FIRE-3 in patients with RAS wild-type status.

Merck Serono submitted that the independent review of scans of tumour response were made available to blinded reviewers who assessed early tumour shrinkage (ETS: expressed as a greater than 20% reduction in size at week 6), depth of response (DpR: expressed as the largest measured reduction in tumour size throughout the treatment cycle) and ORR (complete plus partial response). All results favoured FOLFIRI/cetuximab;

	FOLFIRI/ cetuximab	**FOLFIRI/ bevacizumab**	**p value**
ORR	72.5%	55.5%	0.0063
ETS	69.2%	47.4%	0.0006
mDpR	48.6%	32.2%	0.003

Merck Serono submitted that these results seemed to indicate that FOLFIRI/cetuximab led to an earlier and deeper tumour response compared with FOLFIRI/bevacizumab, and could also help to explain the improved survival advantage of 7.5 months seen with the cetuximab treatment arm in FIRE-3 in the subset of patients with RAS wild-type status.

Merck Serono submitted that therefore that the results of the analysis of FIRE-3 subsets were based upon mechanistic rationale, and included patients for whom cetuximab was an appropriate treatment, whilst also demonstrating in those patients for whom resistance was predicted, either no clinical benefit or indeed a negative effect as an add-on to chemotherapy.

Merck Serono submitted that also rational explanations for improved survival in the cetuximab treatment arm in those patients for whom cetuximab therapy was most appropriate ie those with no RAS mutations.

Merck Serono submitted that other clinical studies were also due to report; in particular the CALGB 80405 study. Interim results of patients with KRAS wild-type status had been presented at ASCO in June of this year. The top-line results did not repeat the observations in patients receiving FOLFIRI/cetuximab as per the FIRE-3 study. During the assessment by the EMA of the CRYSTAL and FIRE-3 data, the CALGB study and interim results were noted. Also noted was the fact the analysis of the results by RAS status had not yet occurred and these analyses were required in order to evaluate properly the results.

Merck Serono submitted that within this particular framework the CHMP had accepted the proposed

Variable/statistic	**RAS wild-type Cetuximab plus FOLFIRI (N=171)**	**Bevacizumab plus FOLFIRI (N=171)**	**RAS mutant Cetuximab plus FOLFIRI (N=92)**	**Bevacizumab plus FOLFIRI (N=86)**
OS				
months, median	33.1	25.6	20.3	20.6
(95% CI)	(24.5, 39.4)	(22.7, 28.6)	(16.4,23.4)	(17.0, 26.7)
Hazard Ratio (95% CI)	0.70 (0.53, 0.92)		1.09 (0.78, 1.52)	
p-value	0.011		0.60	
PFS				
months, median	10.4	10.2	7.5	10.1
(95% CI)	(9.5, 12.2)	(9.3, 11.5)	(6.1, 9.0)	(8.9, 12.2)
Hazard Ratio (95% CI)	0.93 (0.74, 1.17)		1.31 (0.96, 1.78)	
p-value	0.54		0.085	
ORR				
%	65.5	59.6	38.0	51.2
(95% CI)	(57.9, 72.6)	(51.9, 67.1)	(28.1, 48.8)	(40.1, 62.1)
Odds Ratio (95% CI)		1.28 (0.83, 1.99)		0.59 (0.32, 1.06)
p-value		0.32		0. 097

OS = overall survival time; PFS = progression-free survival time; ORR = objective response rate

updates to the SPC in terms of the benefit-risk for the efficacy data from FIRE-3 and it had also recommended submission of data from CALGB 80405 in relation to RAS status when available. Consequent to the positive opinion from the CHMP on 26 June 2014, and with respect to FIRE-3 data, the SPC for cetuximab included the following (section 5.1);

Points of appeal

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 months in mCRC RAS Wild-Type Patients When Compared with Bevacizumab: New Analysis of FIRE-3 AIO Study'

Merck Serono noted that the Panel had ruled a breach of Clause 7.2 since it was considered that the headline was not a fair reflection of the overall data in that it had not been placed within the context of the study's primary outcome. Merck Serono submitted that the context of the headline was very specific in that it stated very clearly RAS wild-type patients, and did not refer to the broader ITT population of KRAS wild-type patients in which the primary outcome had previously been reported. This was because the KRAS wild-type population was known to have patients with mutations beyond the KRAS EXON 2 mutations (which had been excluded following a protocol amendment in October 2008) and therefore contained a patient population predicted to be resistant to cetuximab. Consequently the primary endpoint on the basis of the intention-to treat (ITT) population would not be an accurate reflection of the clinical conclusions that could be drawn. It would be irrational to treat a patient with known RAS mutations with cetuximab; hence it was not rational to include such patients in an analysis of the potential clinical benefits of such a treatment, even though it might be statistically sound to do so. The RAS wild-type population referred to within the headline was therefore precise. The headline clearly stated that the analysis was 'New'; in other words not the first presentation of results.

Merck Serono submitted that clinicians who treated patients with metastatic colorectal cancer were well aware of the development of RAS testing and the implications of such testing in terms of efficacy of EGFR targeted therapies in defined patient populations. The headline provided new information which could help inform their clinical decisions. Further, the results of the comparison complained of was now incorporated into the licence for cetuximab that it was accurate and hence not misleading, and Merck Serono appealed the Panel's ruling of a breach of Clause 7.2.

2 First bullet point in press release; 'New data from a pre-planned analysis of the FIRE-3 study show an increase of median overall survival from 25.6 months to 33.1 months (p=0.011)

Merck Serono noted that a breach of Clause 7.2 had been ruled since the Panel considered that it was not sufficiently clear at the outset that the analysis had been exploratory, and further that such analyses should not be used as the basis for a robust comparison of medicines, and hence the material had been insufficiently complete to enable the recipient to form their own opinion.

Merck Serono submitted that although statistically sound, the analysis of the primary endpoint in the ITT population could lead to clinically unsound conclusions in that the ITT patient population contained a subset of patient that would be resistant to treatment with cetuximab. Since the initiation of that study there had been a protocol amendment to exclude patients with KRAS mutation (of EXON 2). Consequently the ITT population was modified from that originally envisaged. Since that amendment new knowledge regarding the importance of RAS testing, expanded beyond KRAS EXON 2, had been made available, and as such the clinical comparison of the two medicines (cetuximab and bevacizumab) in the ITT population was no longer valid. The clinically meaningful comparison as presented within the press statement was between cetuximab in a non mutant RAS population and the comparator in the same patient population.

Merck Serono submitted that given the evolution of RAS testing and previous amendments to several trials in patients with metastatic colorectal cancer to exclude a KRAS mutant population, it argued that clinicians who treated patients with mCRC were well used to interpretation of analysis of patient subsets under these circumstances, and were able to determine the value of such analyses on their own. Merck Serono therefore appealed the Panel's rulings on this point, and reminded the Appeal Board that the information presented was accurate for the population defined, and this information was now incorporated into the licence for cetuximab.

Merck Serono submitted that Roche had also alleged a breach of Clause 7.4 stating that Merck Serono had not addressed sufficiently their [Roche's] concerns that the sub-group analysis needed to be accounted for statistically to avoid bias from multiple analyses. The Panel ruled that 'On balance and on this very narrow point' the bullet point was not capable of substantiation and hence ruled a breach of Clause 7.4.

Merck Serono submitted that such statistical analyses had indeed been undertaken, and had been scrutinised by the EMA, following which the results of the comparison complained with were now incorporated into the licence for cetuximab. The comparisons made within the bullet point were validated and therefore appealed the Panel's ruling on this point.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

Merck Serono submitted that in reaching its ruling on the above quotation the Panel had alluded to its previous comments with '... regard to the data from the FIRE-3 study showing a 7.5 month increase in median overall survival when using Erbitux plus FOLFIRI as compared with using bevacizumab plus FOLFIRI in metastatic colorectal', and consequently extrapolated these previous findings to the above quotation from Professor Heinmann.

The Panel stated that '... the quotation was misleading as within the context of the median survival data it applied disproportionate weight to the results thereby exaggerating Erbitux's properties and consequently did not encourage the product's rational use'. The Panel thus ruled breaches of Clauses 7.2, 7.10, and 10.2, and also noted its comments applied to Clause 22.2 and similarly ruled a breach of that clause.

Merck Serono submitted that it had argued that the information presented within the press statement was accurate, not misleading, capable of substantiation, and now integral within the licence for cetuximab and consequently it appealed the Panel's rulings.

Additionally Merck Serono submitted that it had argued for rational use of cetuximab based upon RAS status and had presented information on median survival specific to that patient population. This was for a smaller patient population than the licence allowed for at that time (KRAS EXON 2 wild-type), and represented the (smaller) patient population now reflected in the current licence. The update to the licence occurred in December 2013 and was based in part upon these data.

Merck Serono submitted that Professor Heinmann's quotation also continued 'Together with insights from other recent relevant studies, these results suggest that 1st line treatment of RAS wild-type patients should include an anti-EGFR therapy'. The press statement advocated rational prescribing in a specific patient population, rather than the contrary, and therefore Merck Serono appealed the Panel's ruling on this point and consequently appealed the Panel's rulings of a breach of Clause 22.2.

5 Overall

Merck Serono had noted the Panel's comments regarding breaches of Clause 9.1 and in particular Clause 2. The Panel had noted that '... it was very important that press releases about sensitive issues such as survival in cancer were fair, factual and not misleading,' and further that 'the press release had failed to reflect the study's primary endpoint'. Based upon the arguments expounded above Merck Serono submitted that the information regarding survival contained within the press statement was fair, factual and did not mislead. The survival data had subsequently been scrutinised by the EMA and included into the licence for cetuximab. This data was also clearly stated to relate to patients with RAS wild-type tumours, a subset from the FIRE-3 ITT population and therefore not applicable to the broader population in whom the primary analysis had been performed. It had also been stated within the press release that the primary endpoint of the study had not been achieved. Merck Serono rejected Roche's allegation of prejudicing patient safety, and again noted that the survival comparison complained of had been incorporated into the licence for cetuximab. Merck Serono submitted that its actions in releasing the press release at issue on 28 September 2013 did not reflect a lack of the high standards expected from the pharmaceutical industry, nor did it bring discredit to the industry; Merck Serono therefore appealed the Panel's ruling of breaches of Clauses 9.1 and 2.

RESPONSE FROM ROCHE

Before it commented on the specifics of Merck Serono's appeal, Roche stated that it wanted to be clear on its motivation for making this complaint. From the start, the objective was to gain commitment from Merck Serono to cease the use of unfounded claims of Erbitux superiority over Avastin in the first-line treatment of patients with RAS wild-type metastatic colorectal cancer (mCRC) on the basis of an exploratory analysis of a secondary endpoint within a sub-group of a sub-group of patients in the FIRE-3 clinical trial (i.e. the 'RAS wild-type' sub-group of the 'evaluable patient' sub-group). Furthermore, Roche had sought commitment from Merck Serono that it would not make overt claims on the sub-group analysis or include the data in any materials without fully contextualising the analysis in question.

Roche submitted that unfortunately, Merck Serono persistently refused to accept that it had breached the Code and this resulted in the matter being referred to the PMCPA. Importantly, Roche had never questioned the fact that clinicians were interested in comparisons between Avastin and Erbitux in RAS wild-type populations, however it asserted that this did not mean that less robust analysis could be presented as having greater validity simply because it was 'interesting'.

Roche stated that Merck Serono's appeal appeared to be based on an assertion that it was appropriate to use the FIRE-3 exploratory sub-group analysis in question in isolation and without full context for two principal reasons:

1 the Erbitux licence had since been restricted to the population included in the exploratory analysis.

2 the results of the exploratory analysis had apparently now been accepted by the EMA for inclusion into the Erbitux SPC – Merck Serono's implication appeared to be that the EMA review of the data and decision to allow it to be included in the SPC somehow gave it greater statistical validity than would normally be afforded to an exploratory sub-group analysis.

Roche alleged that these arguments were flawed and should make no difference to the rulings on the case for several reasons:

i) The PMCPA guidance on appeal procedures clearly stated that 'it must have been possible to substantiate a claim etc on the day it was made'. When the press release was issued the Erbitux licence matched the intention-to-treat (ITT) population of the FIRE-3 trial so was used the subsequent licence restriction was not relevant.
ii) The argument that the sub-group analysis would soon be in the SPC should hold no weight at all for rulings on materials issued in the past because when a company examined a press release to ensure it did not contravene

the Code, this was based on being able to substantiate the information at the time of examination/approval.

iii) Regardless of the above point, the notion that inclusion in the SPC made an exploratory sub-analysis more robust because it had been scrutinised by the EMA was simply not true. This did not alter Merck Serono's obligation to represent the data in a fair, balanced and contextualised manner.

iv) Independent guidance on the use of secondary endpoints and sub-group analyses (including guidance from the EMEA) supported point iii above by requiring caution with interpreting such data. Clearly when representing data which is based on both a secondary endpoint and in an exploratory sub-group in a trial which failed to meet its primary endpoint, the need for such caution would be even greater:

- EMEA Committee for Proprietary Medicinal Products (CPMP) advice: 'Points to consider on multiplicity issues in clinical trials' (2002):
  - Section 2.1.2 clarified that no confirmatory claims could be based on secondary endpoints in trials where the primary endpoint had not been met
  - Section 3.2 reiterated this point
  - Section 3.3: highlighted that further studies would be needed in this situation
- International Conference on Harmonisation (ICH) E9 guidelines: 'Statistical Principals for Clinical Trials' (1998):
  - Section 5.7 was clear on the need for caution when making treatment efficacy conclusions based solely on exploratory sub-group analyses
- Publication authored by Robert O'Neill of the Food and Drug Administration (FDA): 'Secondary endpoints cannot be validly analyzed if the primary endpoint does not demonstrate clear statistical significance' (1997):
  - Argued that caution was needed when making inferences for secondary endpoints when a trial has failed to meet its primary endpoint.

Licence updates:

Roche alleged that the update to the Erbitux licence to restrict its use to RAS wild-type patients (December 2013) only occurred after the press release was issued (September 2013) and so the FIRE-3 ITT population reflected the licensed population for Erbitux when the press release was issued and so was of very high clinical relevance.

KRAS and RAS proteins:

Roche alleged that this section of the Merck Serono appeal built the argument that reporting of outcomes by different RAS mutation status was important. This extensive section of the appeal missed the crux of the complaint and the Panel ruling which objected to the use of exploratory sub-group analysis to make unequivocal claims, and also the use of this analysis without full contextualisation.

Evolution of RAS testing:

Merck Serono commented that care should be exercised in drawing absolute clinical conclusions from primary endpoints in ITT populations which contained a subset of patients with RAS mutations making them resistant to Erbitux therapy. Roche alleged that this was presumably an attempt to justify why the ITT population primary endpoint results were not included in the press release. This argument was flawed for two reasons:

1 Roche alleged that the primary endpoint results in the ITT trial population were critical to set the context of the exploratory sub-group analysis both from a clinical and statistical perspective, especially when the exploratory analysis was not consistent with the outcome of the overall trial which failed to meet its primary endpoint for demonstrating superiority of Erbitux over Avastin in overall response rate (ORR).
2 Roche alleged that as already stated, the ITT population for FIRE-3 reflected the licensed indication for Erbitux at the time of the press release. Roche questioned the relevance of the OPUS and CRYSTAL post-hoc analyses to this appeal. RAS analysis for the CRYSTAL and OPUS trials were not reported at the time the press release was issued, meaning that the data provided in Merck Serono's appeal on OPUS and CRYSTAL was irrelevant as it was retrospective justification. Furthermore, these analyses compared Erbitux plus chemotherapy with chemotherapy alone so did not specifically address the question of whether Erbitux plus chemotherapy was superior to Avastin plus chemotherapy in the first-line treatment of mCRC.

Roche alleged that importantly, the point made by Merck Serono that dismissing such exploratory analysis on the basis of purely statistical grounds would not be appropriate clinically and could affect patient care missed the point of the core complaint and the Panel ruling: the requirement to not make overt claims on the basis of the analysis and to fully contextualise it did not constitute dismissing such exploratory analyses. The use of unsubstantiable and misleading claims and the omission of full contextualisation which could have a negative impact on patient care.

Analysis of FIRE-3

Roche alleged that Merck Serono's detailed summary of FIRE-3 only further supported its arguments of the importance of providing full context whenever the trial results were discussed. Roche asked the Appeal Board to contrast the full results of the trial and the complex discussion in Merck Serono's appeal with the selective claims and relative prominence given to data included in the press release as Roche believed this spoke for itself.

Roche noted that Merck Serono proceeded to discuss the results of FIRE-3 in its appeal and unequivocally state the OS difference of 7.5 months in the RAS exploratory sub-group analysis that this was not a chance finding. How would Merck Serono know this in view of the EMEA and FDA guidance mentioned

earlier which highlighted the potential for 'false positive' results in such analyses? The guidance from these independent bodies asserted that further prospective trials should be undertaken to validate such findings. In fact, the interim primary endpoint results from the CALGB 80405 trial (mentioned by Merck Serono) showed no difference between the two arms, reinforcing the possibility that the OS difference seen in the KRAS wild-type population of FIRE-3 might have been a false positive result. This clearly added further questions as to the validity of further sub-analyses of this secondary endpoint in FIRE-3.

Roche alleged that experience was that the results of FIRE-3 had caused significant confusion in the clinical community precisely because they were not consistent with the existing evidence base and (by Merck Serono's own admission) raised some key questions specifically on the validity of the OS sub-group analysis for RAS wild-type patients. The questions of how an OS advantage could be demonstrated in the absence of any difference in PFS, and why the Kaplan-Meier curves only started to separate long after cessation of first-line treatment were ones for which there were no conclusive scientific explanations. The reality was that there were three possibilities:

1 The OS results from FIRE-3 study sub-group analysis were chance findings
2 The OS results were not a chance finding but were the result of something other than the first-line treatment
3 The OS results were due to a real effect of first-line Erbitux.

Roche alleged that crucially, there was no way of knowing which of the above was true without a well-planned, prospective randomised, controlled trial (RCT) in RAS wild-type patients as part of a confirmatory strategy. It was important for patients that treatment decisions were not based on reverse-analysis of studies in isolation, but instead were appropriately informed by prospective RCTs, with less robust analysis represented accurately and objectively in clear context.

Roche alleged that Merck Serono had attempted to further justify its belief that Erbitux was driving the OS difference seen in FIRE-3 by introducing the PEAK study at this point as supporting evidence. It was important to note that the phase II PEAK trial did not investigate Erbitux but a different EGFR inhibitor. Within the publication itself it was explicitly stated that it did not plan to test any formal hypotheses and therefore it was conducted to look for trends and for opportunities to potentially launch a subsequent, prospective phase III trial. As such, it did not provide evidence that the OS results in FIRE-3 were due to a real effect of Erbitux as implied by Merck Serono.

Roche alleged that overall, regardless of the nuances within the data, what was clear from both Merck Serono's appeal and Roche response was that this was currently an area with no clear answers and as such, Merck Serono's simplistic and unbalanced representation of the data, and unequivocal claims of superiority in its press release was clearly at odds with this and could seriously mislead the audiences.

Points of appeal

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'

As commented earlier, Roche alleged that these were numerous reasons why it considered that Merck Serono's grounds for appeal were flawed:

- Much of Merck Serono's appeal was irrelevant as it was based on retrospective information/ data
- The fact that the ITT results had been reported previously did not justify omitting them in the press release because all items needed to comply with the Code in their own right
- The headline claim was based on an exploratory sub-group analysis which by definition was hypothesis-generating – not a sound basis for making an overt claim of superiority – the context for this was insufficiently prominent or lacking altogether
- Merck Serono argued in its appeal that 'it would be irrational to treat a patient with known RAS mutations with cetuximab (Erbitux)' yet this important patient safety-related point was omitted from the press release which focussed on the argument for why RAS wild-type patients should receive Erbitux
- Merck Serono's justification that 'clinicians who treated patients with mCRC were well aware of the development of RAS testing and the implications of such testing in terms of efficacy of EGFR targeted therapies in defined patient populations' was flawed on two levels:
  - Even if true this would not negate the requirement of the Code to provide fair and balanced information
  - Merck Serono had confirmed that the press release was issued to 40 medical and pharmaceutical titles, 23 health journalists at national print and online titles and 16 freelance health journalists. Clearly not all of these recipients could be expected to have the necessary depth of understanding of the mCRC treatment environment. This point seemed to suggest confusion within Merck Serono as to the audience and intention of the press release.

2 First bullet point in press release: 'New data from the pre-planned analysis of the FIRE-3 study show an increase of median overall survival from 25.6 months to 33.1 months (p=0.011)'

Roche alleged that Merck Serono's appeal appeared to argue that its representation of the data was acceptable because the RAS analysis was a more 'clinically meaningful' comparison. However interesting or clinically relevant an exploratory analysis was (pre-planned or otherwise) it did not change the fact that the analysis was exactly that - an exploratory analysis. By definition, such analyses should be used to generate hypotheses

which might be validated as primary endpoints in ITT populations through appropriately powered, prospective, randomised clinical trials - the results of which might then validate whether the exploratory analysis was simply a chance finding or not. None of the arguments presented by Merck Serono made a material difference to the Panels ruling.

Roche alleged that furthermore, it was a post-authorisation safety requirement by the EMA that Merck Serono was obligated to submit the results of the FIRE-3 RAS analysis, and this would be incorporated into the Erbitux SPC over 9 months after the issue of the press release. Therefore this did not mean that this superiority claim in the press should be considered capable of substantiation at the time of issue. Aside from this, the important point still remained that inclusion in the Erbitux SPC still would not justify, validate or substantiate an overt claim of Erbitux superiority over Avastin based on an exploratory sub-group analysis.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

Roche alleged that again, the imminent inclusion of the FIRE-3 RAS analysis into the Erbitux SPC was retrospective and therefore not relevant. Furthermore even following SPC inclusion, this quotation continued to be misleading as it still applied disproportionate weight to the exploratory sub-group analysis results and thereby exaggerated Erbitux's properties, thus not encouraging its rational use.

Roche alleged that in addition, NHS England Cancer Drugs Fund data provided evidence that the above quotation did not represent the views of the majority of the clinical community in England since the relative proportions of applications by clinicians for patients to access Avastin and Erbitux for the first-line treatment of mCRC did not indicate a significant change since the FIRE-3 results were presented. This view was also supported by the National Comprehensive Cancer Network (NCCN) Guidelines on Colon Cancer (Version 3.2014) which were critical of the FIRE-3 trial and indicated the need to await further data from other studies to conclude whether these were differences in efficacy between Avastin and Erbitux in relevant patient populations.

5 Overall

Roche alleged that Merck Serono's appeal against the Panel's ruling of breaches of Clauses 2 and 9.1 again centred around its overarching points commented on above earlier. Again, Roche felt strongly that these arguments were both retrospective and irrelevant in that an exploratory sub-group analysis still needed to be clearly and overtly placed into appropriate context, regardless of whether it was included in an SPC or not. None of Merck Serono's arguments justified the use of a hypothesis-generating exploratory sub-group analysis to make unbalanced, uncontextualised and misleading claims around a sensitive issue such as survival in cancer.

Roche noted that Merck Serono had not appealed Point 3 above, thus accepting that it had breached the Code in this regard. This misrepresentation of the data (by implying equivalent efficacy with Avastin in a population within the Avastin licence but outside of the Erbitux licence, based on a retrospective pooled analysis of two different populations of RAS mutations from two different time points) could have potentially serious consequences for patient safety.

Furthermore, Roche noted through its appeal that Merck Serono repeatedly asserted that KRAS wild-type patient populations included a sub-group or patients with RAS mutations who were highly unlikely to respond to Erbitux. Merck Serono used this point to build an argument that this somehow justified its decision to not include full, overt context of the exploratory sub-group analysis in its press release. Roche was confused by this argument as it seemed to raise an important question: if Merck Serono was aware of this at the time of the press release (and would like this to be taken into account in the appeal) then why did it focus exclusively on claims of superiority over Avastin in the material, and omit any mention of this important point relating to patient safety in the press release – instead stating in the press release that 'no new safety signals were observed'?

Additionally, Roche stated that it had raised concerns with Merck Serono and the PMCPA that claims similar to those ruled in breach in this case were being used by Merck Serono in promotional materials. Merck Serono stated that the claims were always set in context and since Roche was not able to provide evidence to the contrary the Panel was unable to rule on this. Roche was now in possession of promotional materials (example provided) which made overt promotional claims on the FIRE-3 exploratory sub-group analysis without, as Merck Serono had indicated, providing full and appropriate context. This suggested a concerning misrepresentation of the data across multiple communication channels. (This material was not subject of the appeal; both parties were so advised.)

Overall, Roche considered that the Panel's ruling of breaches of Clauses 9.1 and 2 were entirely justified as Merck Serono's appeal arguments were predominantly retrospective and even if taken into consideration, they still did not justify the overt claims and lack of full, clear and prominent contextualisation of exploratory sub-group analysis which formed the basis of the breaches of the Code in this case.

APPEAL BOARD RULING

The Appeal Board noted that this was clearly a complex area. As the FIRE-3 study had progressed it had started to become clear that patients with RAS wild-type mCRC responded better to therapy than those with RAS mutations. The analysis at issue in the press release involved only the RAS wild-type patients (n=342) and not the original ITT population (n=592). Although the Erbitux marketing authorisation had been restricted to patients with

RAS wild-type mCRC, this was not the case when the press release was issued on 28 September 2013. In that regard the Appeal Board considered that only the data that was available on that date could be relied upon to substantiate the content of the press release.

1 Heading: 'Merck Serono's Erbitux Significantly Extends Survival by 7.5 months in mCRC RAS Wild-Type Patients When Compared With Bevacizumab: New Analysis of FIRE-3 AIO Study'

In the Appeal Board's view, it was not clear that the new analysis referred to in the bold, prominent heading was an exploratory, retrospective, sub-group analysis of the secondary endpoint of the study. There was a strong possibility that the heading would be incorrectly assumed to refer to the primary endpoint. It was not clear from the outset that the FIRE-3 study had failed to meet its primary endpoint; this was only stated in the third paragraph on page 2.

The Appeal Board noted that when the press release was issued, Merck Serono had one finding in a retrospective analysis of a secondary endpoint that suggested a possible interesting effect in a sub-group of mCRC patients. The Appeal Board doubted whether the study was powered to show whether or not this finding was due to chance and thus a further study would be required to confirm the results. Insufficient information had been provided to enable the reader to properly assess how much weight to attach to the presented secondary endpoint findings. The Appeal Board considered that the heading was misleading as alleged and it upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

2 First bullet point in press release: 'New data from the pre-planned analysis of the FIRE-3 study show an increase of median overall survival from 25.6 months to 33.1 months (p=0.011)'

The Appeal Board considered that its comments above at Point 1 were relevant here. The Appeal Board noted that the exploratory nature of the analysis was not stated. The sub-group analyses had not been placed in the context of the study's failure to achieve its primary endpoint. The Appeal Board considered that 'New data from a pre-planned analysis...' implied that this was the ITT population when it was not. The Appeal Board noted that Merck Serono's representatives at the appeal had described the new data as both a retrospective finding and a pre-planned analysis which was confusing. The Appeal Board could see no evidence that the analysis was pre-planned. The Appeal Board considered that the bullet point was misleading as alleged; not enough information had been presented to enable readers to form their own opinion of the therapeutic value of Erbitux. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board considered that although it had concerns as to whether the analysis was sufficiently powered, the bullet point was nonetheless factually correct and thus on balance, on this very narrow point, was capable of substantiation. No breach of Clause 7.4 was ruled. The appeal on this point was successful.

4 Page 2, Paragraph 4: 'Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'

The Appeal Board noted the full statement referenced to the FIRE-3 principal investigator, on page 2 of the press release stated 'These new data from the Phase III study FIRE-3 show a 7.5-month increase in median overall survival to 33.1 months when using 1st line Erbitux plus FOLFIRI as compared to using bevacizumab plus FOLFIRI in metastatic colorectal cancer. Such a prolongation is a paradigm shift in mCRC treatment since the introduction of monoclonal antibodies'. The Appeal Board considered that the FIRE-3 principal investigator had referred to the increase in the time of median overall survival as the 'paradigm shift'. However, this claim did not refer to the fact that the patient population at issue was restricted to those with wild-type RAS. In the Appeal Board's view the claim appeared to apply to all mCRC patients and that was not so. The Appeal Board was also concerned that the claim strongly implied that the findings were clinically meaningful yet in effect, when the press release was issued, they were no more than suggestive of a potential effect.

The Appeal Board noted its comments and rulings above and considered that the quotation was misleading as it gave undue weight to the median overall survival data given that it came from an exploratory, sub-group analysis. The Appeal Board noted that by contrast, a presentation given by Professor Heinmann had referred to the overall survival data in the context of the failed primary endpoint in the ITT group. The Appeal Board considered that the quotation, within the context of the press release, exaggerated Erbitux's properties and implied that the results were true for all mCRC patients and as such did not encourage the rational use of the product. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.10 and 10.2. The appeal on this point was unsuccessful.

The Appeal Board further considered that if the press release was found on the Internet by mCRC patients (or their carers), it might give them, particularly those without RAS wild-type mCRC, unfounded hopes about their potential treatment and it thus upheld the Panel's ruling of a breach of Clause 22.2. The appeal on this point was unsuccessful.

5 Overall

The Appeal Board noted its rulings of breaches of the Code above. It also noted the Panel's rulings of breaches in Point 3 which were not appealed. It considered that Merck Serono had failed to maintain high standards. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board noted that both it and the Panel (Point 3 above) had considered that the press release did not encourage the rational use of Erbitux. The Appeal Board also considered that the failure of the press release to refer to relevant contra-indications (also noted by the Panel at Point 3 above) raised concerns with regard to patient safety. In the Appeal Board's view, it was extremely important for patients, and the NHS, that press releases about sensitive issues such as survival in cancer were not misleading. Overall, the Appeal Board noted its comments above and the nature of the breaches of the Code ruled and decided to uphold the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **17 March 2014**

Case completed **10 October 2014**
