ROCHE/DIRECTOR v MERCK SERONO

Alleged breach of undertaking

Roche alleged that Merck Serono had breached its undertaking given in Case AUTH/2705/3/14 with regard to a presentation in July 2015 of clinical trial data for Erbitux (cetuximab) to a meeting of the Cancer Drugs Fund (CDF). Roche submitted that, as in the material at issue in Case AUTH/2705/3/14, a September 2013 press release, clinical data had not been presented in context of other data or its (lack of) statistical significance. Roche alleged a breach of Clause 2.

The licence for Erbitux changed in December 2013 such that it was now indicated, *inter alia*, for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer (mCRC). When the press release was issued in September 2013, the licence was wider in that Erbitux was for use in patients with EGFR-expressing, KRAS wild-type mCRC.

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

As the complaint was about an alleged breach of undertaking, it was taken up by the Authority in the name of the Director as the Authority was responsible for ensuring compliance with undertakings.

Roche stated that Merck Serono's presentation in an open forum of other companies, lay members of cancer charities and clinicians, began with an overview of the data it proposed to cover. This included its two registration studies for cetuximab in combination chemotherapy (CRYSTAL and OPUS) and data from the FIRE-3 and CALGB studies.

FIRE-3 was presented first and one slide showed the overall survival but did not explain that this was an exploratory secondary endpoint nor that the study failed to meet its primary endpoint. There were no other slides presented for this study to better understand how the patients in this analysis were arrived at, including whether the analysis was appropriately powered, and whether the correct statistical analysis was used.

Roche stated that as previously ruled in breach of the Code, not providing this study specific information was misleading for the audience regarding the significance of the data. In contrast to Case AUTH/2705/3/14, where the press release included a clarifying statement that the data was exploratory, the presentation did not make this clear.

The FIRE-3 data was also not placed in context of the CALGB data which was designed to look at the specific question regarding the comparison [of cetuximab vs bevacizumab]. Regarding the Merck Serono defence at appeal of the significance of data included in the summary of product characteristics (SPC), Roche noted that the CALGB data was included in the cetuximab SPC immediately below and juxtaposed to the FIRE-3 data: this served to represent the FIRE-3 data in the full context of all clinical data available for cetuximab in this indication.

Roche noted that the CALGB data was included later in the presentation but the scientifically important aspect of discordant results with FIRE-3 was again omitted. The original registration data for cetuximab for this indication was presented later.

At the end of the presentation the chairman of the CDF panel asked the rest of the panel to disregard the portion that focused on the head-to-head studies between Avastin and cetuximab because of the discordant results between FIRE-3 and CALGB data. The chairman also stated that the presentation of the data in comparison to Avastin was not necessary, since this was no longer funded in England for the patient population being discussed. This comment, and the inclusion in the presentation, implied that the CDF panel believed Merck Serono had included an unsubstantiated comparison to a Roche medicine, and misled as to the correct clinical context for the use of cetuximab.

Roche noted that whereas the press release at issue in Case AUTH/2705/3/14 was targeted towards a medical audience and the broader press, the presence of lay observers from cancer charities ought to be considered, this had again occurred in an intentionally non-promotional context, high standards needed to be maintained. In any context, and at the heart of Case AUTH/2705/3/14, all data wherever used or presented had to be fair, balanced, accurate, in context, and not misleading.

The detailed response from Merck Serono is given below.

With regard to Case AUTH/2705/3/14 the Panel considered that the press release 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 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 which was upheld on appeal.

In relation to the bullet point in the press release which read, '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) …' the Panel considered that its general comments above in relation to the heading of the press release were relevant. 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 which was upheld on appeal.

Turning to the present case, Case AUTH/2789/8/15, the Panel noted Merck Serono's submission about the differences between the press release and the material now at issue ie a presentation made to the CDF panel to support the continued use in England of Erbitux in the treatment of mCRC. A copy of the presentation, together with a much larger body of material, had to be submitted to the CDF panel ahead of the meeting. Merck Serono had 15 minutes on the day to make its presentation which, in the Panel's view, it would do on the assumption that the CDF panel members had read the material previously submitted. Although Roche submitted that others including lay members of cancer charities were present at the meeting, the Panel considered that the presentation was, nonetheless, directed solely at the CDF panel.

The Panel noted that slide 2 of the presentation set out the therapeutic indication for Erbitux and highlighted that it was for use in patients with RAS wild-type mCRC. Slide 4 illustrated how the Erbitux licence had evolved over time. Up until 2008, Erbitux was licensed for use in all mCRC patients based on the results from the CRYSTAL and OPUS studies. From 2008 until January 2014 Erbitux was licensed for use in patients with KRAS wild-type mCRC (approximately 55% of all mCRC patients) based on the results from, *inter alia*, FIRE-3. From January 2014 the licence was further restricted to patients with RAS wild-type mCRC (approximately 45% of all mCRC patients) and it was clearly stated on the slide that this was as a result of, *inter alia*, a subgroup analysis of the FIRE-3 study.

The Panel noted that Roche referred in particular to slide 10 headed 'FIRE-3: median Overall survival: RAS wild-type patients' which depicted the probability of overall survival over time. The data showed a benefit for FOLFIRI plus Erbitux vs FOLFIRI plus Avastin. It was made clear that overall survival was a secondary endpoint and hazard ratios and confidence intervals were given. Two separate footnotes in very small print stated that the data was in 'KRAS and NRAS exon 2, 3 and 4 wild-type' and that 'Erbitux (cetuximab) is only indicated in RAS wild-type mCRC (KRAS & NRAS wild-type)'. The Panel noted that the data for the RAS wild-type subgroup from the FIRE-3 study was now included in the Erbitux SPC. In that regard the data had been accepted by the regulatory authorities. In the Panel's view, the patient population suitable for treatment with Erbitux was clearly defined at the outset of the presentation together with an explanation of the clinical data which supported its use in successively restricted populations over time. Subsequent slides which referred to the results of FIRE-3 referred to 'RAS wild-type patients' which in the Panel's view, the audience to whom the presentation was addressed ie the CDF panel, would realise was a subset of FIRE-3. Slide 20 clearly stated the primary endpoint of the FIRE-3 study showed no statistical difference between Erbitux plus FOLFIRI vs Avastin plus FOLFIRI in the intention to treat (ITT) population of KRAS wild-type mCRC patients. The Panel considered it would have been helpful if this information appeared earlier in the presentation.

The Panel considered that there were important differences between the press release and the materials currently at issue and the audiences to whom they were directed. The Panel noted that since the press release had been issued (September 2013), the marketing authorization for Erbitux had changed significantly in that the licensed indication was now restricted for use in patients with RAS wild-type mCRC. As the FIRE-3 study had progressed it became clear that patients with RAS wild-type mCRC responded better to therapy than those with RAS mutations. To support the restricted licence, the Erbitux SPC (last revised June 2014) now included results from the FIRE-3 study with regard to the RAS wild-type population (n=342) and not the ITT group (n=592). In that regard the Panel did not consider it unreasonable for Merck Serono only to refer to the smaller group; indeed to have referred to the ITT group might have been misleading as many of those patients would now not be suitable for Erbitux treatment.

The Panel noted the change in the marketing authorization for Erbitux in December 2013 and overall considered that the content of the presentation at issue, the context in which it was used and the audience to whom it was directed were all significantly different to the press release considered in Case AUTH/2705/3/14 such that it was not closely similar and thus the presentation was not caught by the undertaking previously given. No breaches of the Code were ruled including Clause 2.

Roche Products Ltd alleged that Merck Serono Limited had breached its undertaking given in Case AUTH/2705/3/14 with regard to the presentation of clinical trial data for Erbitux (cetuximab). The material at issue in Case AUTH/2705/3/14 was a press release; the material now at issue was a presentation given to the Cancer Drugs Fund (CDF).

The licence for Erbitux changed in December 2013 such that it was now indicated, *inter alia*, for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer (mCRC). When the press release was issued in September 2013, the licence

was wider in that Erbitux was for use in patients with EGFR-expressing, KRAS wild-type mCRC.

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

As the complaint was about an alleged breach of undertaking, it was taken up by the Authority in the name of the Director as the Authority was responsible for ensuring compliance with undertakings.

COMPLAINT

Roche explained that as part of the CDF's review of a number of medicines that were available for funding in England, the CDF panel held two days of meetings, 29 and 30 July, during which pharmaceutical companies could present clinical data to support the continued use of the medicine. This was the second such panel meeting and the pharmaceutical company engagement process was the same both times. Merck Serono presented the same clinical case at the original meeting in December and therefore knew the format of the meeting and the appropriateness of data for inclusion in the presentation.

To facilitate this meeting, companies were invited to submit supporting clinical data by 16 July; such data would subsequently be presented at the meeting. It was not mandatory to submit a presentation or to present, and not all companies took up this opportunity.

The presentations, which were to last approximately five minutes, were made in an open forum consisting of other companies, lay members of cancer charities, and clinicians (the full attendee list was not publicly available). The CDF panel consisted of a sub-committee of Clinical Reference Group members. Following the presentation, the panel could ask questions and the company could respond to those. The panel members took notes to help to inform their decision making in a subsequent closed meeting, where a clinical score would be attributed to each medicine per specific indication. The clinical score was critical in determining whether a medicine would stay funded for use in England beyond around December 2015. Therefore, the presentation of the clinical data was of the highest importance given the public scrutiny; it must of course be factually accurate, not misleading, able to be substantiated and placed within the correct clinical context of treatment within the UK and England.

Roche noted that Merck Serono provided evidence for cetuximab in accordance with its CDF listing.

Since companies could not provide their presentation on the day, and to follow process, Merck Serono sent its slides to the CDF panel before the presentation. Printed copies of the presentation were provided for the panel before the meeting opened, and separate from the verbal presentation.

Roche noted that a member of Merck Serono medical team presented the cetuximab data and began by discussing the first-line mCRC data in combination with chemotherapy.

Roche alleged a breach of Clause 29 with regard to the undertaking given in Case AUTH/2705/3/14 in respect of the content of the pre-submitted slides and the omission of context, the omission of either the CALGB interim analysis (no statistical significance) or the subsequent final analysis (still no statistical difference), and the misleading over-emphasis of the clinical data during the presentation.

Roche noted that in Case AUTH/2705/3/14 a breach of Clause 2 was ruled, upheld at appeal, given the nature of the multiple breaches relating to the presentation of the FIRE-3 data in a press release. Roche asserted that the same actions and omissions had occurred in an exceptionally high profile forum which could only reduce confidence in the pharmaceutical industry.

Roche stated that Merck Serono opened its presentation with an overview of the data it proposed to cover. This included its two registration studies for cetuximab in combination with irinotecan and oxaliplatin-based combination chemotherapy respectively (CRYSTAL and OPUS). Merck Serono also stated that it was going to include data from the FIRE-3 and CALGB studies.

The first study presented was FIRE-3 (rather than the registration study, CRYSTAL) and one slide showed the overall survival Kaplan-Meier curve without any qualification either on the slide, or verbally, that this was an exploratory secondary endpoint for a study, nor that it did not meet its primary endpoint. There were no other slides presented for this study to better understand how the patients in this analysis were arrived at, including whether the analysis was appropriately powered, and whether the correct statistical analysis was used, since the primary endpoint was negative.

As previously ruled in breach of Clause 7.2, not providing this study specific information was misleading for the audience regarding the significance of the data. An important additional contrast to Case AUTH/2705/3/14, where the press release included a statement to clarify that the data was exploratory, albeit significantly distant from the prominent statement, in this presentation neither verbally nor on the slides was this contextualizing point made clear.

The FIRE-3 data was also not placed in context of the CALGB data which was designed to look at the specific question regarding the comparison [of cetuximab vs bevacizumab]. Regarding the Merck Serono defence at appeal of the significance of data included in summary of product characteristics (SPC), Roche noted that the CALGB data was included in the cetuximab SPC immediately below and juxtaposed to the FIRE-3 data: this served to represent the FIRE-3 data in the full context of all clinical data available for cetuximab in this indication.

Roche noted that the CALGB data was included later in the presentation but the scientifically important aspect of discordant results with FIRE-3 was a second time omitted and not highlighted. The original registration data for cetuximab for this indication was presented later.

At the end of the presentation for first-line mCRC, the chairman of the CDF panel, an oncologist, asked the rest of the panel to disregard the portion that focused on the head-to-head studies between Avastin and cetuximab because of the discordant results between FIRE-3 and CALGB data.

The chairman also stated that the presentation of the data in comparison to Avastin was not necessary, since this was no longer funded in England for the patient population being discussed. The impression left by this comment, and the inclusion in the presentation, was that the panel believed Merck Serono had included this to make an unsubstantiated comparison to a Roche medicine, and to mislead as to the correct clinical context for the use of cetuximab.

In Case AUTH/2705/14 breaches were ruled. Roche was concerned once again that high standards were not upheld with regard to this presentation in an area where Merck Serono had previously been found in breach and as the chairman had to request the CDF panel to disregard information this brought discredit to and reduced confidence in the pharmaceutical industry.

Roche submitted that someone from another pharmaceutical company who was present, and very closely aware and following the therapy area and science, spoke to a Roche individual at the meeting, to state that it was clear that Merck Serono's actions were exactly those described in Case AUTH/2705/3/14 as related to misleading and over-emphasising the clinical significance of FIRE-3, and not placing it in context for the audience. The individual also highlighted that a breach of Clause 2 was ruled, and he/she were extremely surprised to see the same actions happening in this high-profile setting.

Roche noted that whereas the press release at issue in Case AUTH/2705/3/14 was targeted towards a medical audience and the broader press, the presence of lay observers from cancer charities ought to be considered, this had again occurred in an intentionally non-promotional context, but the high standards required by Clause 9.1 still needed to apply. In any context, and at the heart of Case AUTH/2705/3/14, all data wherever used or presented had to be fair, balanced, accurate, in context, and not able to mislead.

Roche stated that in conclusion, a pharmaceutical company's presentation of data, when relied upon by national public organisations, must be able to withstand the highest level of public scrutiny and scientific rigor. This required maintaining the highest standards as set out in Clause 9.1, identified as a Code breach relating to the presentation of the FIRE-3 data, and here the undertaking to maintain high standards Roche asserted was a breach of Clause 29. It was both disappointing and fortuitous that the chairman of the panel publicly asked panel members to disregard this aspect of data presentation.

RESPONSE

Merck Serono stated that it took compliance with the Code extremely seriously and understood the importance of complying with undertakings given under the Code. The company provided details of the actions it took to comply with the undertaking in Case AUTH/2705/3/14. This included, without limitations, withdrawing all materials in breach of the Code as a result of the rulings in that case, ensuring all subsequent promotional materials provided enough information to ensure the reader could form a rational opinion of the use of the medicine, by training personnel on the details of the case and issuing guidance to reduce the risk of anything similar occurring in the future.

Merck Serono did not believe that the presentation it gave at the CDF or any of the materials and submissions sent to the CDF in preparation for the meeting breached the undertaking given in Case AUTH/2705/3/14 or Clauses 2 and 9.1 of the Code as outlined below.

1 The licence for Erbitux had changed materially since Case AUTH/2705/3/14

When the press release was published, Erbitux's marketing authorization was not restricted to patients with RAS wild-type mCRC. The Appeal Board noted in its ruling that 'The analysis at issue in the press release involved only the RAS wild-type patients (n=342) and not the original ITT populations (n=592). Although the Erbitux marketing authorization 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'. The rulings in Case AUTH/2705/3/14 were therefore made in that context.

Merck Serono stated that the current complaint must been seen in light of the marketing authorization in place in July 2015 when the submission and presentation was made to the CDF.

In December 2013, the indication was restricted to patients who had RAS wild-type mCRC as new safety information had become available from a retrospective subset analysis of data from a randomised, multicentre phase II study (OPUS) of cetuximab plus (oxaliplatin-containing) FOLFOX4 chemotherapy vs FOLFOX4 alone in people with previously untreated mCRC. In the OPUS study, patients with RAS mutations who were randomly assigned cetuximab plus FOLFOX4 had inferior survival, progression-free survival and objective response rates than did those assigned FOLFOX4 alone. As a consequence of this information, in February 2014 the CDF reimbursement for Erbitux in the treatment of mCRC was restricted to RAS wild-type patients only.

Further post-hoc analyses of the interaction between RAS mutation status and treatment outcome in the pivotal first-line phase III cetuximab trials CRYSTAL and FIRE-3 (the study at issue in the press release) were still ongoing when the indication was amended in December 2013. When completed, these analyses were included in the Erbitux SPC in July

2014, demonstrating that their validity and clinical relevance was *de facto* accepted by the regulators. Section 5.1 of the SPC did not present the intention to treat (ITT) population results for these studies including FIRE-3 (the study at issue), but summarised the efficacy results in tables which compared only the RAS wild-type population (as per indication) with the RAS mutant population (not indicated). The tables started with overall survival, then progression free survival and then objective response rate and displayed duration (months), hazard ratios, their confidence intervals and associated p values. There was no discussion of the failed primary endpoint in the ITT population of FIRE-3.

As such, the results of the ITT population were not directly relevant as many of the ITT population were no longer within the licensed indication for Erbitux. Merck Serono believed that the data it presented at the CDF meeting was not misleading as it was aligned with the Erbitux SPC and the specific CDF reimbursement indication that Merck Serono had been invited to defend. ITT results were simply not under consideration by the CDF.

Merck Serono thus refuted the alleged breach of undertaking (Clause 29) as the licensed indication for Erbitux and the data to support it as described in the SPC was materially different to that which was in place when the press release at issue in Case AUTH/2705/3/14 was issued. For the same reason, Merck Serono did not believe that the presentation given to the CDF or any of the materials submitted to the CDF breached Clauses 2 or 9.1 as high standards were maintained and therefore they did not bring discredit upon, or reduce confidence in, the pharmaceutical industry.

2 Meaningful difference in the materials at issue

Merck Serono noted that the press release at issue in Case AUTH/2705/3/14 was distributed through usual channels to health journalists interested in oncology with the expectation they would share this news story with their readership, many of whom would be the general public.

The presentation now at issue was part of a submission to a national public health organisation, the Chemotherapy Clinical Reference Group, which was an NHS England committee responsible for administering and recommending which medicines were funded via the CDF and made available to NHS patients in England. This body, which occupied a health technology assessment (HTA) role for cancer medicines, assessed cancer medicines if they had been rejected or not yet reviewed by NICE. It did so via a formal process, and its decisions were published. It did not procure medicines. The CDF current standard operating procedures were provided. Merck Serono submitted that as such, the CDF was analogous to bodies described in Clause 1.2 of the Code and both the presentation and the submission to the CDF fell outside the scope of the Code. For this reason the presentation was not considered promotional and was not certified.

The CDF panel meeting was part of an ongoing process designed to refine the list of medicines authorised for reimbursement through the CDF in England. The CDF panel members had been selected by NHS England for their expertise, judgment and competence in defining criteria and evaluating the available clinical evidence to judge which oncology medicines best met those criteria and warranted investment of NHS expenditure to improve patient outcomes. Companies were invited to defend their current listed status through the submission of an extensive dossier of evidence, with a form aligned to a scoring system designed by the CDF and supported by clinical studies and a full reference pack (a copy was provided). The panel was familiar with the evidence for Erbitux in first-line treatment of mCRC in RAS wild-type patients as it had last assessed it in December 2014, with comparable data being used to support the clinical review.

Following the written submission each company was invited to defend its indications. The presentation time was limited to 5 minutes per indication approved. In the case of Erbitux, 15 minutes were allocated to defend the three CDF approved mCRC indications. Thus the presentation itself formed a limited part of the extensive submission and assessment process. Content of the presentation was focused on efficacy criteria determined by the CDF as of critical importance to determine their score of clinical effectiveness, notably median overall survival, median progression free survival endpoints, safety and quality of life.

Merck Serono submitted that meeting attendees were restricted to CDF panel members, who were the intended audience for the presentation, expert pharmaceutical company personnel and their representatives eg physicians or patient groups who were expert in the field to present their data or add expert opinion. Companies had to register their attendees and staff outside the meeting room ensured only those authorised to attend could do so. A list of CDF panel members who attended the meeting was provided.

Additionally, unlike the press release in Case AUTH/2705/3/14, the presentation now at issue was delivered by a company expert who could talk through the data, clarify any issues and answer the panel's questions. The panel members were all versed in evidence review and familiar with the data as they last reviewed it in December 2014. The panel had received all clinical trial data in advance and were provided with the current Erbitux SPC.

Merck Serono stated that in its view, the presentation and submission provided were appropriate and not misleading given the purpose and context of the meeting, and the knowledge of the members of the CDF panel and other attendees at the meeting, and given that the information presented or provided by Merck Serono was in line with the Erbitux SPC and the CDF listing under discussion. Therefore Merck Serono believed it had complied with Clauses 2, 9.1 and 29.

3 Content of the presentation

Merck Serono stated that the language used in the press release and its tone were substantially different

from the content of the presentation now at issue. The content of the CDF presentation was factual, accurate and not misleading. The presentation also formed part of a larger written submission to defend Erbitux's listing in the CDF for first-line use in RAS wild-type mCRC, in combination with either irinotecan-based therapy or FOLFOX.

Merck Serono noted Roche's assertion that Merck Serono had breached its undertaking because of the content of the slides, the omission of context, the omission of either the CALGB interim analysis (no statistical significance) or final analysis (still no statistical difference) and the misleading over-emphasis of the clinical data during the presentation.

As discussed above, the licensed indications for Erbitux when the CDF submission took place and the context and purpose in which the presentation at issue was made, were materially different from those at the time of the press release. The presentation explicitly focused on treatment of RAS wild-type mCRC patients in line with the licensed indication for Erbitux. This was made clear in the first slide of the presentation, and reinforced in subsequent slides.

The next slide summarised the CDF score applied to the evidence, and made clear exactly which population was being discussed (column headed 'biomarker defined population' with clear RAS wild-type against all first-line studies, and KRAS wild-type against third or fourth). The application of a score by the CDF panel was done in January 2015 which confirmed that the panel had already considered these data. The CDF panel was therefore not only versed in oncology data assessment, but also already familiar with these particular data and all the other evidence submitted in the dossier from the previous submission.

Several studies were discussed in the presentation. For each of them, relevant data in the licensed, RAS wild-type patient population had been achieved through retrospective sub-analyses of studies originally conducted in a wider patient population. Slide 4 highlighted this limitation of the data and explained the relevance of biomarkers and how they informed the interpretation of Erbitux data and its progressively restricted indication. Using the phrase 'subpopulation' made it clear that this was not the ITT population, the results of which were no longer relevant as they included patients who were not within the licensed indication and not being considered by the CDF. Slide 5 highlighted the extent to which this restriction of patient population consistently improved hazard ratios across a number of studies of EGFR inhibitors while also showing that original ITT patient populations were in broader patient sets.

As discussed above, these subgroup analyses had been in the SPC without the need to include the ITT results, which was not the case when the press release was issued in September 2013. This meant that information which could have been construed as misleading at the time should not be construed in the same way today.

Merck Serono submitted that a considerable proportion of the limited time available to present the data was devoted to ensuring a clear understanding that the clinical data subsequently discussed was derived from subgroup analyses of larger studies. In discussion at the end of the presentation, it was confirmed that the RAS wild-type population analyses were retrospective and FIRE-3 was highlighted in this context.

In contrast to Roche's assertion that FIRE-3 was the first study presented, data from the pivotal CRYSTAL study was the first data presented in slide 6. It was used to exemplify the progressive restriction of the Erbitux indication and its concomitant positive effect on risk benefit for the target patient population.

When endpoints for the FIRE-3 study were introduced, all relevant efficacy measures, and their degree of significance were shown (slide 8). When discussing the study design (slide 9), the original patient population, and protocol amendment, primary and secondary endpoints were all listed. After these two slides, the overall survival data in the RAS wild-type subset of patients was then discussed (slide 10) as overall survival was a particularly important endpoint to the CDF, and this subset was the licensed and reimbursed patient population in the UK.

FIRE-3 was subsequently mentioned in slide 20 with the intent to support a consistency of overall survival for Erbitux in combination with chemotherapy in the RAS wild-type subset across a range of studies. In this summary slide, the initial patient population, the primary endpoint and lack of a statistically significant difference were clearly referenced.

Merck Serono noted that Roche asserted that FIRE-3 data were not placed in context of the CALGB data yet it was presented on slide 4, slide 8 (combination with FOLFIRI), slides 15, 17, 18 (combination with FOLFOX) and in the summary slide 20. In each slide, the data were presented factually with appropriate endpoints and statistical analyses represented to allow relevant assessment. Roche's submission that this data was not present was inaccurate.

Merck Serono further noted that Roche asserted that the chairman of the CDF panel asked the panel to disregard the portion that focused on the head-to-head studies between Erbitux-based treatment and bevacizumab-based treatment because of the discordant results between FIRE-3 and CALGB data; Roche believed the impression was that Merck Serono had included this to make an unsubstantiated comparison with a Roche medicine and to mislead as to the correct clinical context for the use of cetuximab although it had provided no evidence for this assertion.

Merck Serono stated that it had a very different impression of commentary and discussion at the end of the presentation. The initial comment from the panel chairman reminded the panel of the limitations of the data which had been openly discussed in the presentation, and highlighted the heightened relevance of direct comparisons with

chemotherapy alone rather than to bevacizumab, as first-line regimens that included bevacizumab in combination with chemotherapy were no longer treatment options in this patient population as they had been removed by the CDF in the December 2014 prioritisation exercise. Finally, the discussion then gave Merck Serono the opportunity to reinforce that data analyses presented were retrospective (including, but not limited to FIRE-3) and to clarify the ongoing NICE assessment of these data and the relevance of Erbitux in other lines of therapy.

Merck Serono submitted that in summary the presentation focused on data which supported the CDF score for the listing under review and took a factual, balanced tone. That the RAS wild-type population analyses for all presented studies was retrospective, was discussed. CRYSTAL, rather than FIRE-3 was the first study for which data was presented. Relevant endpoints, statistical analysis and study design features for the licensed population were included to allow appropriate assessment of the data. CALGB/SWOG data was featured throughout the presentation, with appropriate endpoints and statistical analyses represented to allow relevant assessment. Limitations of the data were appropriately highlighted, both during the presentation and in the discussion. Any comparison made was evidence based and supported by clinical data. Similarly, Merck Serono could see no evidence of misleading the CDF panel as to the correct clinical context for the use of cetuximab as the presentation clearly focused on the licensed indication which was repeatedly listed on the slides.

4 Conclusion

Merck Serono denied the alleged breach of the undertaking given in Case AUTH2705/3/14. It believed it had maintained the high standards set out in Clause 9.1. In the context of a non-promotional meeting, which had a clearly defined format and purpose as set out and solicited by the CDF, the content of the presentation at issue was appropriate, factual, accurate and not misleading. The CDF panel was versed in its field and able to fully understand the data as presented. The presentation ensured the specific subpopulation of mCRC patients for whom Erbitux was indicated was clear and also how that subpopulation was derived though RAS testing on the original trial populations. The presentation, which formed part of a wider submission, was in line with the Erbitux SPC and the CDF listing.

Further, Merck Serono submitted that it approached its obligations under the Code with the utmost seriousness, as demonstrated by its remedial actions following the previous breach.

Merck Serono refuted Roche's allegations that it had acted in breach of Clauses 2, 9.1 and 29 of the Code.

PANEL RULING

The Panel noted that an undertaking was an important document. Companies had to give an undertaking that the material in question and any similar material, if not already discontinued or no longer in use, would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the material previously at issue in Case AUTH/2705/3/14 was a press release which had been sent to medical and pharmaceutical titles, health journalists at national print and online titles and freelance health journalists. 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 which was upheld on appeal.

In relation to the bullet point in the press release which read, '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) …' the Panel considered that its general comments above in relation to the heading of the press release were relevant. 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 which was upheld on appeal.

Turning to the present case, Case AUTH/2789/8/15, the Panel noted Merck Serono's submission about the meaningful differences between the press release and the material now at issue in Case AUTH/2789/8/15 ie a presentation made to the CDF panel to support the continued use in England of Erbitux in the treatment of mCRC. A copy of the presentation, together with a much larger body of material, had to be submitted to the CDF panel ahead of the meeting. Merck Serono had 15 minutes on the day to make its presentation which, in the Panel's view, it would do on the assumption that the panel members had read the material previously submitted. Although Roche submitted that others including lay members of cancer charities were present at the meeting, the Panel considered that the

presentation was, nonetheless, directed solely at the CDF panel.

The Panel noted that slide 2 of the presentation set out the therapeutic indication for Erbitux and highlighted that it was for use in patients with RAS wild-type mCRC. Slide 4 illustrated how the Erbitux licence had evolved over time. Up until 2008, Erbitux was licensed for use in all mCRC patients based on the results from the CRYSTAL and OPUS studies. From 2008 until January 2014 Erbitux was licensed for use in patients with KRAS wild-type mCRC (approximately 55% of all mCRC patients) based on the results from, *inter alia*, FIRE-3. From January 2014 the licence was further restricted to patients with RAS wild-type mCRC (approximately 45% of all mCRC patients) and it was clearly stated on the slide that this was as a result of, *inter alia*, a subgroup analysis of the FIRE-3 study.

The Panel noted that Roche referred in particular to slide 10 headed 'FIRE-3: median Overall survival: RAS wild-type patients' which depicted the probability of overall survival over time. The data showed a benefit for FOLFIRI plus Erbitux vs FOLFIRI plus Avastin. It was made clear that overall survival was a secondary endpoint and hazard ratios and confidence intervals were given. Two separate footnotes in very small print stated that the data was in 'KRAS and NRAS exon 2, 3 and 4 wild-type' and that 'Erbitux (cetuximab) is only indicated in RAS wild-type mCRC (KRAS & NRAS wild-type)'. The Panel noted that the data for the RAS wild-type subgroup from the FIRE-3 study was now included in the Erbitux SPC. In that regard the data had been accepted by the regulatory authorities. In the Panel's view, the patient population suitable for treatment with Erbitux was clearly defined at the outset of the presentation together with an explanation of the clinical data which supported its use in successively restricted populations over time. Subsequent slides which referred to the results of FIRE-3 referred to 'RAS wild-type patients' which in the Panel's view, the audience to whom the presentation was addressed ie the CDF panel, would realise was a subset of FIRE-3. Slide 20 clearly stated the primary endpoint of the FIRE-3 study showed no statistical difference between Erbitux plus FOLFIRI vs Avastin plus FOLFIRI in the ITT population of KRAS wild-type mCRC patients. The Panel considered it would have been helpful if this information appeared earlier in the presentation.

The Panel considered that there were important differences between the press release and the materials currently at issue and the audiences to whom they were directed. The Panel noted that since the press release had been issued (September 2013), the marketing authorization for Erbitux had changed significantly in that the licensed indication was now restricted for use in patients with RAS wild-type mCRC. As the FIRE-3 study had progressed it became clear that patients with RAS wild-type mCRC responded better to therapy than those with RAS mutations. To support the restricted licence, the Erbitux SPC (last revised June 2014) now included results from the FIRE-3 study with regard to the RAS wild-type population (n=342) and not the ITT group (n=592). In that regard the Panel did not consider it unreasonable for Merck Serono only to refer to the smaller group; indeed to have referred to the ITT group might have been misleading as many of those patients would now not be suitable for Erbitux treatment.

The Panel noted the change in the marketing authorization for Erbitux in December 2013 and overall considered that the content of the presentation at issue, the context in which it was used and the audience to whom it was directed were all significantly different to the press release considered in Case AUTH/2705/3/14 such that it was not closely similar and thus the presentation was not caught by the undertaking previously given. No breach of Clause 29 was ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2 of the Code.

During its consideration of this case the Panel noted Merck Serono's submission that the CDF was analogous to bodies listed in an exemption to Clause 1.2 (NICE, the All Wales Medicines Strategy Group (AWMSG) and the Scottish Medicines Consortium (SMC)) and as such the presentation and the submission to the CDF fell outside the scope of the Code; the presentation was not considered promotional and was not certified. The Panel noted that Clause 1.2 of the Code provided that information supplied by pharmaceutical companies to national public organisations, such as NICE, the AWMSG and the SMC was exempt from the Code provided it was factual, accurate and not misleading. The Panel noted that the CDF panel was a subgroup of the Chemotherapy Clinical Reference Group; neither was listed in the exemption to Clause 1.2. Although the list was not exhaustive and other closely similar bodies might be recognised as national public bodies, in the Panel's view the exemption should be narrowly construed. The Panel noted Merck Serono's submission that the Chemotherapy Clinical Reference Group did not procure medicines. The Panel noted, however, that according to the CDF standard operating procedures, the role of the CDF panel was to manage the CDF on behalf of the Chemotherapy Clinical Reference Group. The CDF was intended to pay for the procurement of medicines. The CDF panel would monitor expenditure and support the management of the CDF budget to maximise overall clinical value to NHS patients and value for money to NHS England. Given its role, the Panel queried whether the CDF panel was a national public organisation similar to those listed in the exemption to Clause 1.2 and thus whether the presentation and submission ought to have been certified. The Panel requested that Merck Serono be advised of its concerns in this regard.

Complaint received **14 August 2015**

Case completed **3 November 2015**