LILLY v ROCHE

Promotion of Tarceva

Lilly complained about the promotion of Tarceva (erlotinib) by Roche. The items at issue were a leavepiece, an advertisement in Oncology Times and a sponsored feature in Oncology News. Tarceva was indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with stable disease after 4 cycles of standard platinum-based first-line chemotherapy. It was also indicated for treatment in locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Lilly supplied Alimta (pemetrexed).

Lilly stated that the items at issue all claimed that Tarceva was licensed for use as 'first-line maintenance' therapy in advanced NCSLC. Lilly had further complained to Roche that the front of the leavepiece stated that Tarceva was 'now licensed for first-line maintenance in patients with stable disease', without clarifying that the specific indication was for the treatment of advanced NSCLC.

The treatment algorithm for patients with advanced lung cancer was complex. Lilly explained that first-line and maintenance treatment of locally advanced or metastatic NSCLC were two distinct and specific indications; first-line being the indication of induction treatment, usually with platinum-based combination chemotherapy, followed by maintenance treatment which was the initiation of treatment in patients whose disease had not progressed immediately following first-line therapy. The majority of the patients were treated with first-line treatment options and observed until disease progression became evident, at which stage licensed second-line treatment options could be considered. Until recently, no medicine was specifically licensed for the maintenance setting. The first product licences for maintenance treatment were granted for Alimta in 2009 and Tarceva in 2010. Alimta was indicated as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease had not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.

Currently, licensed medicines were available for first-line, second-line or maintenance. Patients whose disease had progressed after first-line or maintenance therapy were eligible for second-line treatment. Roche had argued that 'first-line maintenance' was used to distinguish from second-line maintenance. However, a licence for second-line maintenance *per se* did not exist.

Given the multiple treatment variations, possible treatment algorithms and the inherent potential for confusion, the Tarceva and Alimta indications, as defined by the European regulators, were very specifically worded. Lilly alleged that the claim 'first-line maintenance' was ambiguous, misleading and not consistent with the Tarceva SPC.

In the absence of a clear statement on the front of the leavepiece of the intended therapeutic use, Lilly believed that physicians might believe that Tarceva could be used in unlicensed NCSLC settings (eg stage IIIA patients) or indeed in any other cancer. Lilly alleged that such omission amounted to misleading promotion outside the licensed indication in breach of the Code.

The Director noted that the leavepiece had been withdrawn by Roche during inter-company dialogue. Inter-company dialogue had been partially successful. The new leavepiece however, still included the claims cited by Lilly above and so these were referred to the Panel.

The detailed response from Roche is given below.

The Panel noted that the Alimta SPC referred to its use as first-line treatment, maintenance treatment following first-line chemotherapy and second-line treatment in NSCLC. Tarceva was indicated for maintenance treatment following first-line chemotherapy and for treatment following the failure of at least one prior chemotherapy regimen. The Panel noted that the Tarceva leavepiece included the claims 'Now licensed for first-line maintenance in patients with stable disease' and 'Tarceva now approved as first-line maintenance'. There were other references to 'first-line maintenance'. 'First-line maintenance' was not used in the Tarceva SPC. This appeared to be a term used by Roche to describe Tarceva's use in stable disease following platinum doublet chemotherapy. In the Panel's view, the use of the term 'first-line maintenance' therapy was ambiguous; it implied that there might be a product for second-line maintenance or that Tarceva should be used for maintenance therapy before any other therapies also licensed for maintenance. Neither was so. The Panel noted Roche's submission that 'first-line maintenance' was cited in the medical literature. Nonetheless the promotion of a medicine must not be inconsistent with the particulars listed in its SPC. The Tarceva SPC did not refer to 'first-line maintenance'. In that regard the Panel considered that the use of 'first-line maintenance' was misleading and inconsistent with the Tarceva SPC.

The product had not been licensed or approved as 'first-line maintenance' as stated. Reference to the product licence in this regard appeared to validate Roche's description. Breaches of the Code were ruled. This ruling was appealed by Roche.

The Panel considered that the absence of the licensed therapeutic use on the front page of the new leavepiece was not in itself misleading. The front of the leavepiece did not mention any type or stage of cancer. In this regard it was not inconsistent with the SPC and no breach of the Code was ruled.

The Panel noted that the advertisement was headed 'A lifeline after first-line chemotherapy in advanced NSCLC' followed by a photograph of the palm of a hand beneath which was the claim 'Now licensed for first-line maintenance in patients with stable disease*'. The explanation for the asterisk appeared in smaller typesize immediately beneath the claim 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of platinum based first-line chemotherapy'. The Panel noted that it was a principle under the Code that claims should be capable of standing alone without relying on footnotes to provide further explanation.

The Panel considered that the claim in the advertisement 'Now licensed for first-line maintenance in patients with stable disease' was in breach of the Code for similar reasons to the leavepiece. This ruling was appealed by Roche.

The Panel noted that each page of the four page article 'First-line maintenance (1LM) treatment: a new strategy to treat advanced NSCLC' was headed, in a small font size, 'Sponsored Feature'. The author was a consultant medical oncologist. At the foot of the first page was a statement that the article was commissioned by Roche Products Ltd, that medical writing support was provided by Darwin Healthcare Communications, paid for by Roche and that the views expressed were those of the author. At the foot of pages 2-4 of the article was the highlighted statement 'This article is supported by Roche Products Ltd'.

The Panel noted that Roche had not commented on whether or not the sponsored feature was promotional material. The approval certificate stated that the signatories considered it was not promotional and was in accordance with, *inter alia*, the Code.

The Panel noted that whether a company was responsible for sponsored material depended on a number of factors including whether the material was initiated by a third party, although that in itself did not automatically absolve the company from responsibility under the Code for its content. It had previously been decided in relation to material aimed at health professionals that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable it if had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Panel noted that the ZINC job summary indicated that Roche had been asked to sponsor a topical article in the Oncology News and that it approached the author and asked him to write an article about first-line maintenance. It was stated that the author retained full editorial control. The objective was to inform readers of the rational and clinical data behind first-line maintenance treatment in NSCLC. In the 'Notes' section it was stated that there were plans to get reprints of the article for the HSSs to provide to customers.

The Panel thus considered that there was no arms length arrangements between Roche and the other parties. Roche was inextricably linked to the content of the article. Although the author had retained editorial control, he had been chosen by Roche and the company had defined the scope of the article. The article referred to erlotinib and bevacizumab (Roche's product Avastin). In the Panel's view, Roche's failure to recognise that the article constituted promotional material showed a lack of understanding of the requirements of the Code.

The Panel referred to its comments above in relation to the leavepiece and noted that the article stated that erlotinib could be used for 'first-line maintenance' treatment when such an indication was not referred to in the SPC. A breach of the Code was ruled. This ruling was appealed by Roche.
The Appeal Board noted that the Code required that a medicine must be promoted in accordance with the terms of its marketing authorization and that promotion must not be inconsistent with the particulars listed in the medicine's SPC. The Appeal Board further noted that the Code did not require claims to use identical wording to that found in the SPC. In the Appeal Board's view one of the effects of the Code was to protect patient safety and to stop a patient receiving a medicine when it was inappropriate for them to do so.

The Appeal Board noted that Tarveva materials were targeted at physicians experienced in the use of anti-cancer therapies. In the Appeal Board's view, experienced oncologists would not be misled as to Tarceva's position in the management of NSCLC. The Appeal Board did not consider that, to an oncologist, 'first-line maintenance' might imply 'first-line treatment' or that 'first-line' in this context implied the preferred choice. The materials at issue all referred to the use of Tarceva after first-line chemotherapy.

The Appeal Board did not consider that claims in the leavepiece regarding 'first-line maintenance' were either misleading or inconsistent with the particulars listed in the Tarceva SPC as alleged. In the Appeal Board's view, having read the leavepiece, experienced oncologists would be in no doubt which patients should receive Tarceva. The Appeal Board ruled no breach of the Code. The Appeal Board considered its comments and rulings similarly applied to the advertisement and the sponsored feature. The appeal on all points was thus successful.

Eli Lilly and Company Limited complained about the promotion of Tarceva (erlotinib) by Roche Products Limited. The items at issue were a leavepiece (ref TARC00522), an advertisement in Oncology Times (ref TARC00568a) and a sponsored feature in Oncology News (ref TARC00592). Inter-company dialogue had failed to resolve the matter.

Tarceva was indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with stable disease after 4 cycles of standard platinum-based first-line chemotherapy. It was also indicated for treatment in locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Lilly supplied Alimta (pemetrexed).

COMPLAINT

Lilly stated that the items at issue all claimed that Tarceva was licensed for use as 'first-line maintenance' therapy in advanced NCSLC.

Lilly's initial email to Roche related to the use of 'first-line maintenance' in all three promotional items for erlotinib. Lilly also pointed out to Roche that when the flaps of the leavepiece were unfolded, the first part of the claim 'Tarceva as first-line' separated from the second part, 'maintenance therapy'.

Lilly further complained to Roche about the absence of the intended therapeutic use of Tarceva on the front of the leavepiece. This item stated that Tarceva was 'now licensed for first-line maintenance in patients with stable disease', without clarifying that the specific indication was for the treatment of advanced NSCLC.

The summary of product characteristics (SPC) for Tarceva stated that: 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with stable disease after 4 cycles of standard platinum-based first-line chemotherapy'.

The treatment algorithm for patients with advanced lung cancer was complex. Lilly explained that first-line and maintenance treatment of locally advanced or metastatic NSCLC were two very distinct and specific indications; first-line being the indication of induction treatment, usually with licensed platinum-based combination chemotherapy, followed by maintenance treatment which was the initiation of treatment in patients whose disease had not progressed immediately following first-line therapy. The majority of the patients in routine clinical practice were treated with first-line treatment options and observed until disease progression became evident, at which stage licensed second-line treatment options could be considered. Until recently, no medicine was specifically licensed for the maintenance setting. The first product licences for maintenance treatment were granted for Alimta in 2009 and Tarceva in 2010. Alimta was indicated as monotherapy for the maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease had not progressed immediately following platinum-based chemotherapy. First-line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel.

Currently, licensed medicines were available for first-line, second-line or maintenance indications. Patients whose disease had progressed after first-line or maintenance therapy were eligible for second-line treatment. Roche had argued that 'first-line maintenance' was used to distinguish from second-line maintenance. However, a licence for second-line maintenance *per se* did not exist.

Given the multiple treatment variations, possible treatment algorithms and the inherent potential for confusion, the wording of the Tarceva and Alimta indications, as defined by the European regulators, were very specific. Lilly alleged that the claim for 'first-line maintenance' was not consistent with the Tarceva SPC, created ambiguity in the mind of the prescriber and misled.

Roche had agreed in inter-company correspondence that in the leavepiece the separation of the first part of the claim 'Tarceva as first-line' from the second part, 'maintenance therapy,' might confuse and mislead physicians. In that regard Roche had therefore withdrawn and amended the leavepiece accordingly. Roche had however, not amended its use of 'first-line maintenance' to describe the licensed indication for Tarceva. Lilly nevertheless believed that the use of 'first-line maintenance' when referring to the indication for Tarceva, was misleading and inconsistent with the particulars listed in its SPC, as it implied that Tarceva was licensed for use in first-line initial treatment, rather than for maintenance treatment in patients who had already received first-line treatment with another chemotherapy. Lilly believed that given the prominence of the 'first-line maintenance' claims readers would be misled as to the licensed indication. Lilly therefore alleged that 'first-line maintenance' was in breach of Clauses 3.2 and 7.2.

Additionally, in response to Lilly's concern regarding the lack of information about the intended therapeutic use on the front of the leavepiece, Roche

had also stated that it would not make any changes. In the absence of a clear statement of the intended therapeutic use, Lilly believed that physicians might believe that Tarceva could be used in unlicensed NCSLC settings (eg stage IIIA patients) or indeed in any other cancer. Lilly therefore considered that such omissions amounted to promotion which was misleading and outside the licensed indication in breach of Clauses 3.2 and 7.2.

Whilst Lilly agreed that differences of opinion could exist in a clinical and academic setting to define what constituted first-line and maintenance indications, these arguments were not valid in a promotional setting. Promotional claims needed to be consistent with the SPC. The SPC did not refer to 'first-line maintenance' while defining the indication for Tarceva. Lilly alleged that the promotional use of 'first-line maintenance' over-shadowed other explanations and over-interpreted the SPC definition.

Lilly had suggested that alternative terminology such as 'maintenance after first-line treatment' instead of 'first-line maintenance' might be acceptable, but Roche wished to continue to use the latter.

RESPONSE

Roche explained that the standard treatment for inoperable NSCLC was systemic therapy, most commonly with cytotoxic medicines (chemotherapy). Chemotherapy was usually given in courses of several cycles followed by a period off treatment for patients who had benefited. The terms 'first-line maintenance', 'second-line' treatment etc were generally used to describe successive courses with second-line treatment only given after disease progression. For example, in the UK, as elsewhere the standard first-line chemotherapy was 4 cycles of chemotherapy with a two medicine regime including a platinum-containing medicine ('platinum doublet chemotherapy').

Recently there had been interest in providing ongoing treatment to patients who had benefited from first-line chemotherapy. Alimta and Tarceva were indicated for such use.

The Tarceva SPC stated that 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy'. Roche had used 'first-line maintenance' to describe this indication which it believed was consistent with the SPC and precisely and concisely defined the use of Tarceva in its licensed indication – to maintain the benefits achieved after successful first-line chemotherapy.

However Lilly appeared to believe that 'first-line maintenance' was misleading and implied that Tarceva could be used as a substitute for first-line chemotherapy. This was clearly not so, as without a first-line treatment that stabilized disease, there could be no benefit to maintain.

In Roche's initial response to Lilly, Roche agreed that the chemotherapy given before maintenance 'first-line', (sometimes referred to as 'induction') and 'maintenance' were distinct indications. However, Roche did not agree that 'first-line maintenance' implied use as an initial first-line therapy. Roche believed that 'first-line treatment' and 'first-line maintenance' clearly and unambiguously described different licensed indications and were not misleading or confusing. Indeed, Roche believed that 'first-line maintenance' was less ambiguous then the unqualified term 'maintenance'. It allayed confusion about the appropriate positioning of Tarceva (which was specifically approved as a maintenance treatment after first-line but not after second-line or subsequent chemotherapies) whilst remaining consistent with the marketing authorization and SPC.

Furthermore, Roche noted that the SPC stated 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy' where the maintenance setting was prior to progression of disease and the institution of second-line treatment (this had also been acknowledged by Lilly in its complaint), thus rendering it as treatment in the first-line setting. As such, Roche believed that 'first-line maintenance' was wholly consistent with the marketing authorization and SPC, and therefore not in breach of Clause 3.2 and 7.2.

Roche noted that 'first-line maintenance' was commonly used in clinical practice not only in NSCLC (Patel *et al* 2009) but also in other tumour settings such as breast cancer, haematological malignancies, and had been cited quite often in the medical literature including that produced by Lilly for pemetrexed which was also licensed in the maintenance setting for the treatment of NSCLC.

The Tarceva SPC clearly stated that 'Tarceva treatment should be supervised by a physician experienced in the use of anti-cancer therapies'. Roche was confident that physicians experienced in the management of NSCLC would not confuse first-line maintenance with first-line treatment.

Subsequent to this initial dialogue, Lilly suggested alternative wording 'maintenance therapy after first-line treatment' which it considered was 'less ambiguous' than 'first-line maintenance'. Roche deemed both of these terms acceptable in defining the appropriate positioning of Tarceva as first-line maintenance therapy in NSCLC. However, Roche believed that the preferred terminology of 'first-line maintenance' was more specific since it described maintenance treatment given before first progression whereas 'maintenance therapy after first-line treatment' was less specific and could cover the institution of maintenance therapy following any

line of treatment including after second and subsequent lines of chemotherapy where it was unlicensed.

Roche noted Lilly's concern about the separation of the first part of the claim 'Tarceva as first-line' from the latter part 'maintenance therapy' when the leavepiece was unfolded. In response to this Roche had submitted that this could, unintentionally introduce ambiguity and had agreed to withdraw and amend the leavepiece to ensure that this separation did not occur. Withdrawal had taken place and the amended leavepiece was provided.

Lilly had also complained during inter-company dialogue that the claim on the front of the leavepiece 'Now licensed for first-line maintenance in patients with stable disease' did not clearly describe the intended therapeutic use of Tarceva. Although this issue was only raised in the final letter to Roche, and as such had not been adequately discussed through inter-company dialogue, Roche was happy to have this resolved as part of this complaint.

Roche believed that when reviewed in its entirety, the positioning of Tarceva in advanced NSCLC as first-line maintenance therapy following first-line chemotherapy in patients with stable disease was made quite explicit in several places in the leavepiece including; the first tag line before the leavepiece was unfolded, the design of the SATURN trial and the exact wording of the licensed indication, the title of the overall survival Kaplan Meier curve, and the clear diagrammatic depiction of the place of Tarceva in the treatment pathway for patients with advanced NSCLC which thus left little room for misinterpretation. In addition, it was clearly stated on the front of the leavepiece where the prescribing information could be found detailing the licensed indication for Tarceva in accordance with the SPC and marketing authorization. As such, Roche denied a breach of Clauses 3.2 and 7.2.

Roche noted that it had not intended to promote Tarceva as upfront 'first-line' therapy in advanced NSCLC and therefore great care had been taken in the generation of claims and materials relating to the licensed indications for Tarceva.

1 Leavepiece

PANEL RULING

The Director noted that the leavepiece (ref TARC00522) had been withdrawn by Roche during inter-company dialogue as Roche had agreed with Lilly's concern that it could unintentionally introduce ambiguity. Inter-company dialogue had been partially successful, as acknowledged by Lilly, and so that aspect of the complaint was not referred to the Panel. The new leavepiece (TARC00601) however, still included some of the claims at issue in the original leavepiece. Inter-company dialogue had not been successful in relation to all the claims and as they were still being used the outstanding matters in relation to the new leavepiece were referred to the Panel.

The Panel noted that the Alimta SPC referred to its use as first-line treatment, maintenance treatment following first-line chemotherapy and second-line treatment in NSCLC. Tarceva was indicated for maintenance treatment following first-line chemotherapy and for treatment following the failure of at least one prior chemotherapy regimen. The Panel noted that the Tarceva leavepiece included the claims 'Now licensed for first-line maintenance in patients with stable disease' and 'Tarceva now approved as first-line maintenance'. There were other references to 'first-line maintenance'. 'First-line maintenance' was not used in the Tarceva SPC. This appeared to be a term used by Roche to describe Tarceva's use in stable disease following platinum doublet chemotherapy. In the Panel's view, the use of the term 'first-line maintenance' therapy was ambiguous; it implied that there might be a product for second-line maintenance or that Tarceva should be used for maintenance therapy before any other therapies also licensed for maintenance. Neither was so. The Panel noted Roche's submission that 'first-line maintenance' was cited in the medical literature. Nonetheless the promotion of a medicine must not be inconsistent with the particulars listed in its SPC. The Tarceva SPC did not refer to 'first-line maintenance'. In that regard the Panel considered that the use of 'first-line maintenance' was misleading and inconsistent with the Tarceva SPC. The product had not been licensed or approved as 'first-line maintenance' as stated. Reference to the product licence in this regard appeared to validate Roche's description. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel considered that the absence of the licensed therapeutic use on the front page of the new leavepiece was not in itself misleading. The front of the leavepiece did not mention any type or stage of cancer. In this regard it was not inconsistent with the SPC and no breach of Clauses 3.2 and 7.2 was ruled.

2 Advertisement

PANEL RULING

The Panel noted that the advertisement was headed 'A lifeline after first-line chemotherapy in advanced NSCLC' followed by a photograph of the palm of a hand beneath which was the claim 'Now licensed for first-line maintenance in patients with stable disease*'. The explanation for the asterisk appeared in smaller typesize immediately beneath the claim 'Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of platinum based first-line chemotherapy'. The Panel noted that it was a principle under the Code that claims should be capable of standing alone without relying on footnotes to provide further explanation.

The Panel considered that the claim in the advertisement 'Now licensed for first-line maintenance in patients with stable disease' was in breach of Clauses 3.2 and 7.2 for similar reasons to the leavepiece.

3 Sponsored feature

PANEL RULING

The Panel noted that each page of the four page article 'First-line maintenance (1LM) treatment: a new strategy to treat advanced NSCLC' was headed, in a small font size, 'Sponsored Feature'. The author was a consultant medical oncologist. At the foot of the first page was a statement that the article was commissioned by Roche Products Ltd, that medical writing support was provided by Darwin Healthcare Communications, paid for by Roche and that the views expressed were those of the author. At the foot of pages 2-4 of the article was the highlighted statement 'This article is supported by Roche Products Ltd'.

The Panel noted that Roche had not commented on whether or not the sponsored feature was promotional material. The approval certificate stated that the signatories considered it was not promotional and was in accordance with, *inter alia*, the Code.

The Panel noted that whether a company was responsible for sponsored material depended on a number of factors including whether the material was initiated by a third party, although that in itself did not automatically absolve the company from responsibility under the Code for its content. It had previously been decided in relation to material aimed at health professionals that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable it if had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Panel noted that the ZINC job summary stated in the 'Background/Objective' section that Roche had been asked to sponsor a topical article in the Oncology News and that it approached the author and asked him to write an article about first-line maintenance. It was stated that the author retained full editorial control. The objective was to inform readers of the rational and clinical data behind first-line maintenance treatment in NSCLC. In the 'Notes' section it was stated that there were plans to get reprints of the article for the HSSs to provide to customers.

The Panel thus considered that there was no arms length arrangements between Roche and the other parties. Roche was inextricably linked to the content of the article. Although the author had retained editorial control, he had been chosen by Roche and the company had defined the scope of the article. The article referred to erlotinib and bevacizumab (Roche's product Avastin). In the Panel's view, Roche's failure to recognise that the article constituted promotional material showed a lack of understanding of the requirements of the Code.

The Panel referred to its comments above in relation to the leavepiece and noted that the article stated that erlotinib could be used for 'first-line maintenance' treatment when such an indication was not referred to in the SPC. A breach of Clauses 3.2 and 7.2 was ruled.

APPEAL FROM ROCHE

Roche re-iterated that standard treatment for inoperable NSCLC was systemic therapy, most commonly with cytotoxic medicines (chemotherapy). Chemotherapy was usually given in courses of several cycles followed by a period off treatment for patients who had benefitted. The terms 'first-line treatment', 'second-line treatment' etc were generally used to describe successive courses with second line treatment only given after disease progression. For example, in the UK, as elsewhere the standard first-line chemotherapy for treating NSCLC was 4 cycles of chemotherapy with a two medicine regimen including a platinum-containing medicine ('platinum doublet chemotherapy').

Roche submitted that the division of systemic treatment in first-line, second-line etc, with each new line introduced after disease progression was a well established concept within oncology, it was not terminology coined by Roche and could be found in many SPCs eg pemetrexed, bevacizumab, capecitabine, navelbine and irinotecan. It was well understood by those at whom Tarceva promotional materials were directed ie physicians experienced in the use of anti-cancer therapies. Recently there had been interest in providing immediate ongoing treatment to patients who had benefitted from first-line chemotherapy in order to sustain its benefit, namely 'maintenance therapy', and two medicines were licensed in this situation – Alimta (pemetrexed; Lilly) and Tarceva (erlotinib; Roche). As maintenance therapy was instituted before disease progression (which conventionally defined the need for second-line therapy) immediately following first line chemotherapy it could be considered as a treatment in the first-line setting. Maintenance therapy, by its very nature, could not exist in isolation and was part of a package with the induction chemotherapy that produced the benefit which it was used to maintain.

To clarify NSCLC medicine treatment Roche provided a treatment algorithm which showed the progression from first line to second line.

1 Leavepiece

Roche noted that the Panel had decided that the use of 'first-line maintenance' was ambiguous and that it implied that there might be a product for second-line maintenance or that Tarceva should be used for maintenance therapy before any other therapies licensed for maintenance, in turn it ruled that the use of the term 'first-line maintenance' was in breach of Clauses 3.2 and 7.2 of the Code.

Roche highlighted that, in contrast, Lilly had alleged that 'first-line maintenance' implied that Tarceva was licensed for use in first-line initial treatment.

Roche disagreed on both accounts; it believed that 'first-line maintenance' unambiguously described the appropriate positioning of Tarceva within the treatment pathway for NSCLC ie to maintain the benefit of the first-line chemotherapy to which it was inextricably linked. In this context, it must be remembered that those involved in this area already understood the term first-line chemotherapy. Not to qualify the term 'maintenance' was genuinely ambiguous and gave no indication as to where within the treatment pathway it should be used. The unqualified term would imply that it could be used as maintenance after any line of chemotherapy, which was inconsistent with its marketing authorization

Roche disagreed with the Panel's view that the use of 'first-line maintenance' was problematic because it implied that there might be a product for second-line maintenance. Not only was there no rationale for considering that the licence for one product would influence clinicians' beliefs about where another product was licensed, but Roche understood this complaint was about whether clinicians were clear about Tarceva's licence, not those of other products. Roche submitted that the potential to confuse and mislead health professionals to prescribe Tarceva as 'second-line maintenance' treatment (where it was clearly not licensed) was eliminated by the use of the term 'first-line maintenance' whilst remaining wholly consistent with Tarceva's licensed indication.

Roche also disagreed with the Panel's view in that the use of 'first-line maintenance' implied that Tarceva should be used for maintenance therapy before any other therapies licensed for maintenance. Roche assumed that the Panel formed this view because it considered that 'first-line' was synonymous with 'first-choice' and implied a claim of superiority or priority over other products. As already explained, 'first-line' was used to define systemic treatment administered for NSCLC prior to first disease progression and was well understood by both the regulatory authorities who had endorsed its use in the Tarceva marketing authorization and by clinicians working in the area. It would be perverse to believe that the latter might interpret 'first-line' in the way that Panel appeared to have done.

In relation to Lilly's assertion that 'first-line maintenance' implied that Tarceva was licensed for use in first-line initial treatment, Roche had already asserted that 'first-line' and 'first-line maintenance' were distinct indications and that 'first-line maintenance' was less ambiguous than the unqualified use of 'maintenance'. Furthermore, 'first-line maintenance' inherently implied that 'first-line' treatment had already been instituted for which the benefit achieved could be maintained by the institution of 'first-line maintenance' treatment ie without a first-line treatment that successfully stabilised disease, there could be no benefit to maintain. This was made quite explicit within the leavepiece where several references had been made for the use of Tarceva as 'first-line maintenance treatment in patients with stable disease' which further emphasized Tarceva's place as 'first-line maintenance' therapy in patients who had achieved stable disease following their 'first-line' treatment in concordance with Tarceva's SPC and marketing authorization.

Roche agreed with the Panel that the promotion of a medicine should not be inconsistent with the particulars listed in its SPC and maintained that 'first-line maintenance' was not inconsistent with Tarceva's licensed indication and particulars of its SPC. As explained above, Roche submitted that as maintenance therapy was instituted before disease progression immediately following first-line chemotherapy, it was a treatment therapy in the first-line setting and thus the use of the term 'first-line maintenance' remained consistent with the particulars of the Tarceva SPC. Roche had noted that whilst the claims 'first-line maintenance in patients with stable disease' or 'Tarceva now approved as first-line maintenance' were not verbatim representations of the particulars listed in the SPC ('Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy') they were not inconsistent with the licensed indication as required by the Code. Roche also highlighted that the Code did not require verbatim duplication of the particulars of SPCs to be part of all claims within promotional material for a medicine, but more importantly that all claims should not be inconsistent with the licensed indication and SPC.

The Panel had also noted that Tarceva had not been licensed for 'first-line maintenance' implying that 'first-line maintenance' and 'maintenance' treatment were distinct indications. Roche disagreed with this viewpoint and regarded 'first-line maintenance' as maintenance treatment delivered after successful first-line induction chemotherapy.

Furthermore, Roche submitted that 'first-line maintenance' was widely used and understood by those cancer specialists who might prescribe Tarceva. To support this Roche provided extensive references to illustrate that 'maintenance' and 'first-line maintenance' were used interchangeably to describe the same treatment setting and noted that

one of the references was authored by representatives of Lilly which further validated Roche's assertion that 'first-line maintenance' and 'maintenance' were regarded as the same indication. Roche understood that 'first-line treatment' and 'first-line maintenance treatment' were distinct indications and noted that the wording used within all claims for Tarceva in the maintenance setting ensured full use of 'first-line maintenance' without separation to ensure that health professionals were neither misled nor confused as to the positioning of Tarceva for treating NSCLC.

Since Tarceva had been launched in the maintenance setting Roche had not received any queries regarding the term 'first-line maintenance' and did not believe that confusion existed for clinicians who could prescribe.

For the reasons cited above, Roche submitted that the use of 'first-line maintenance' in the promotional material was wholly consistent with the marketing authorization and SPC, and therefore not in breach of Clauses 3.2 and 7.2.

2 Advertisement

Roche noted that the Panel had considered that the claim 'Now licensed for first-line maintenance in patients with stable disease' was a breach of Clauses 3.2 and 7.2. Roche appealed this ruling for the reasons highlighted above and maintained that 'first-line maintenance' was consistent with Tarceva's licensed indication and particulars of its SPC.

3 Sponsored feature

Roche noted that the Panel had considered that the claim that Tarceva could be used for 'first-line maintenance' was a breach of Clauses 3.2 and 7.2. Roche appealed this ruling for the reasons highlighted above and maintained that 'first-line maintenance' was consistent with Tarceva's licensed indication and particulars of its SPC.

RESPONSE FROM LILLY

Lilly considered that the claim 'first-line maintenance' was not consistent with the Tarceva SPC, was ambiguous, misleading and likely to confuse the reader.

Lilly noted that Roche had produced a flowchart for a possible treatment algorithm for advanced NSCLC. Lilly alleged that in relation to the pemetrexed and erlotinib maintenance licence, first-line induction therapy did not include or encompass maintenance as proposed by Roche in its flowchart. This was an important distinction in the maintenance licence for both medicines; maintenance was stated in the SPCs for both medicines as treatment after first-line therapy in patients who, in the case of pemetrexed achieved a clinical response (complete or partial response or stable disease), or in the case of erlotinib, achieved stable disease. Lilly also noted that both the pemetrexed and erlotinib licenses for maintenance therapy were restricted to patients who had not received those respective medicines as first-line treatment, and therefore it was important to maintain the distinction, as set out in the SPCs, between maintenance and first-line induction therapy, to avoid any confusion that the same medicine could be used from induction through to disease progression.

Lilly noted that Roche had submitted that 'maintenance', as it stood in the licence, required further qualification and inappropriately sought to qualify its precise meaning. The latter was a matter for Roche to take up with the relevant regulatory authorities. The final wording, and the meaning of statements incorporated in the erlotinib SPC were agreed between Roche and the European Medicines Agency, accordingly no further clarification was required. Lilly stated that 'second-line maintenance' had no meaning – if the patient's disease progressed they received some other line of treatment and not maintenance treatment. One of Roche's original arguments for use of the phrase 'first-line maintenance' - that it avoided possible confusion with use in second-line maintenance - was unjustifiable as no licence for second-line maintenance existed.

Further, as acknowledged by Roche, erlotinib was licensed solely for maintenance therapy in patients who had stable disease following first-line therapy with doublet chemotherapy. Therefore a claim of 'first-line maintenance' was inherently confusing even on the basis of Roche's own submission given that erlotinib was not licensed for maintenance treatment in patients who had achieved a complete or partial response following first-line treatment.

Lilly submitted that the Panel's observation that 'first-line maintenance' might imply that erlotinib should be used as a first choice maintenance treatment added further weight to the argument that confusion was likely to arise through use of the phrase.

Lilly noted that it had never suggested to Roche that the Code mandated verbatim use of SPC language. Roche seemed to imply that the only alternative to using 'first-line maintenance' was a verbatim use of SPC language. This was clearly not so, as indicated in inter-company correspondence. Lilly's position had consistently been that Roche should ensure that promotional claims for erlotinib were not inconsistent with the marketing authorization (as per Clause 3.2). Indeed, Lilly had previously suggested to Roche that it could employ the claim 'maintenance treatment after first-line chemotherapy'. Further, as maintenance therapy in advanced NSCLC was a newly approved indication, clarity and consistency of promotional claims with a medicine's SPC was even more important.

Lilly alleged that Roche's reliance on selective publications and clinical opinions was not objective or fair and further misled regarding the correct

interpretation of the licenced indication of erlotinib as stated in its SPC. Roche had used the claim in question to over interpret the SPC for commercial expediency.

APPEAL BOARD RULING

The Appeal Board noted that Clause 3.2 required that a medicine must be promoted in accordance with the terms of its marketing authorization and that promotion must not be inconsistent with the particulars listed in the medicine's SPC. The Appeal Board further noted that the clause did not require claims to use identical wording to that found in the SPC. In the Appeal Board's view one of the effects of Clause 3.2 was to protect patient safety and to stop a patient receiving a medicine when it was inappropriate for them to do so.

The Appeal Board noted that the target audience for the Tarceva promotional material was physicians experienced in the use of anti-cancer therapies. In the Appeal Board's view, experienced oncologists would not be misled as to Tarceva's position in the management of NSCLC. The Appeal Board did not consider that, to an oncologist, 'first-line maintenance' might imply 'first-line treatment' or that 'first-line' in this context implied the preferred choice. The materials at issue all referred to the use of Tarceva after first-line chemotherapy.

The Appeal Board did not consider that claims in the leavepiece regarding 'first-line maintenance' were either misleading or inconsistent with the particulars listed in the Tarceva SPC as alleged. In the Appeal Board's view, having read the leavepiece, experienced oncologists would be in no doubt which patients should receive Tarceva. The Appeal Board ruled no breach of Clauses 3.2 and 7.2. The appeal on this point was successful.

The Appeal Board noted its comments above in relation to the leavepiece and considered that they also applied to the advertisement. The Appeal Board ruled no breach of Clauses 3.2 and 7.2. The appeal on this point was successful.

The Appeal Board similarly considered that the sponsored feature was neither misleading nor inconsistent with the particulars listed in the Tarceva SPC as alleged. No breach of Clauses 3.2 and 7.2 were ruled. The appeal on this point was successful.

Complaint received **19 August 2010**

Case completed **10 November 2010**